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(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

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A PECULIAR TYPE OF ADRENAL CORTICAL DAMAGE ASSOCIATED WITH ACUTE INFECTIONS, AND ITS POSSIBLE RELATION TO CIRCULATORY COLLAPSE

ARNOLD R. RICH

From the Department of Pathology and Bacteriology, The Johns Hopkins Medical School

Submitted for publication September 28, 1943

The purpose of this paper is to direct attention to a peculiar type of injury to the adrenal cortex that occurs not infrequently during severe acute infections produced by various microörganisms, and which may be of importance in contributing to the circulatory collapse that is often a complication of those infections. An examination of the literature shows that an alteration of the type here to be described, which converts the solid cords of cortical cells into gland-like, tubular structures, was noted by several writers in the early part of the present century. Thomas (1) and Dietrich (4) regarded the condition as being the result of a degenerative process. Beckman (3) regarded it as a normal, though irregularly present, state. Demole (2) believed it to be an indication of some particular functional activity of the adrenal. Somewhat later, in 1922, Goormaghtigh (5) described gland-like cavities in the cortex in cases of peritonitis, and he regarded them as being an indication of a hypersecretion of an antitoxic substance. At the time of these earlier observations, the lack of information regarding the function of the adrenal cortex precluded any suggestion of the relation of the lesion to circulatory collapse during infections, and mention of the condition apparently attracted too little attention to render it familiar to pathologists either then or subsequently, as an examination of the standard present-day text-books of pathology and endocrinology will disclose.

The lesion when well developed is a quite extraordinary one, for it results in the conversion of the normally solid cords of cells of the zona fasiculata, and to a lesser degree the zona glomerulosa, into hollow structures resembling renal tubules. These tubular formations may contain, separately or in combination, coagulated protein, fibrin, polymorphonuclear leucocytes, and occasional necrotic cortical cells, or

they may appear empty. The cortical cells that line the "tubules" are often markedly flattened, may contain little lipoid, and often appear to have lost much of their cytoplasm. Figures 2, 3, 4, 5, 6, 7, 8, 9, 14 and 15 illustrate the lesion in its well developed form.

The earliest stage in the development of the lesion that we have been able to recognize appears to consist in necrosis of isolated cells of the cords of the zona fasiculata. The dead cells may have a highly vacuolated cytoplasm, or the cytoplasm may be non-vacuolated and densely eosinophilic (Fig. 10). While cell death occurs in the centers of the cords as well as at the margins, and while death and lysis of central cells doubtless contributes to the formation of some of the "tubules", there is no evidence that the formation of the larger "tubules" results simply from death and lysis of groups of cells in the centers of the cords, leaving marginal cells alive. Rather, the death, shrinkage and lysis of isolated marginal cells permits an exudation of fluid from the adjacent capillary into the space left by the necrotic cells, and the escaping fluid penetrates into the center of the cord and appears to dissect the living cells apart in the long axis of the cord, separating them widely, and thus forming a tubular structure (Figs. 11 and 12). The extent of the dissection varies. In places the fluid extends between the cord cells for a distance equal to that of only a few cell lengths. In other places the separation of the cells by the fluid may occur throughout virtually the entire length of the cord (Figs. 2 and 3). The process ordinarily begins in the outer third of the zona fasiculata, and it may be confined to that region or may extend further inward.

That the fluid occupying the "tubules" has been derived from the blood is indicated by the fibrin threads that are often found within them (Figs. 11, 13, 14, 15). The fact that the cortical cells lie directly against the adjacent capillary wall doubtless renders easy the penetration of fluid from the capillary into the substance of the cord when cells adjacent to the capillary are lost from the cord by necrosis. The exudation of fluid from the capillary is probably stimulated by the irritant effect of the necrotic cells, and the polymorphonuclear leucocytes are doubtless attracted by the dead cells. The flattening out of the cells that line the "tubules" is probably produced in part by the pressure of the fluid exudate. In addition, there can be found suggestive evidence that some of the substance of the damaged cells is shed

into the tubular lumen, somewhat analogous to the loss of substance of the renal tubular epithelium that occurs in cloudy swelling.

All degrees of the above-described process, which may be termed "tubular degeneration" of the adrenal cortex, can be found in different cases. In some, one finds only scattered necrotic cells; in others, focal "tubule" formation; and in others, the most widespread "tubule" formation involving virtually the entire cortex of both adrenals. When well developed, as in Figures 2, 3, 4, 5, 6, 7, and 8, there can be little doubt that the function of the affected cortical cells must be greatly impaired, and it is proper to raise the question as to the significance of this lesion in contributing to the circulatory collapse that occurs in severe cases of the acute infections in which the present lesion makes its appearance. We have repeatedly observed the lesion at autopsy in cases of meningococcal, pneumococcal and streptococcal infection and in diphtheria, in severe cases of all of which infections circulatory collapse of unexplained origin is familiar. In the case of meningococcal infection the Waterhouse-Friederichsen syndrome, in which circulatory collapse occupies a prominent place, is ordinarily attributed to massive bilateral adrenal haemorrhage. While extensive haemorrhage into the adrenals in meningococcal infection is familiar, it is far less frequent in adults than in children; and it has long been our experience that most cases of circulatory collapse occurring in adults during meningococcal infection fail to show at autopsy an amount of haemorrhage sufficient to impair any appreciable amount of the adrenal cortex. In many cases the adrenals show only a few petechial haemorrhages or none at all.

Figures 5, 14 and 15 illustrate one of many such examples. The patient, a white male 39 years old, collapsed while walking on the street, and was brought to the Johns Hopkins Hospital. The blood pressure was 80/40, then became too low to measure, and the patient died an hour and a half later. At autopsy (No. 14853) there was found an early meningococcal meningitis. There were two minute, microscopic haemorrhages in the sections of the adrenals, which were, however, the seat of widespread lesions of the type that forms the subject of the present paper.

Figure 6 illustrates another case of this type in a 5 year old negress, who was brought to the Johns Hopkins Hospital in shock. The pulse

was 180 and feeble; the blood pressure too low to measure; the skin cold and moist. Meningococci were recovered from the blood and spinal fluid. The patient died 12 hours after admission. Only one or two minute, microscopic haemorrhages were found in adrenals at autopsy (No. 15068), but the adrenal cortex showed the illustrated condition.

Figures 2, 3, 10, 11, 12 and 13 illustrate the same situation in a 23 year old white female admitted to Sydenham Hospital with meningococcal meningitis. A diagnosis of Waterhouse-Friedrichsen syndrome was made (B.P. 70/40), and the patient died 16 hours after admission. At autopsy (Johns Hopkins Hospital No. 18205) only two minute, microscopic haemorrhages were found in six sections of the adrenals, which were, however, the seat of extensive cortical lesions of the type illustrated.

Figures 7 and 8 illustrate the lesion in cases of circulatory collapse occurring during pneumococcal and streptococcal infection; and Figure 9, in diphtheria.

It may be objected that adrenal cortical failure can play no rôle in the circulatory collapse that occurs in pneumococcal pneumonia, since studies of patients with lobar pneumonia have shown a retention of sodium chloride rather than a loss. Conditions may, however, be otherwise at the period of circulatory collapse.

It is true that animals survive for some days after adrenalectomy, and this might appear to argue against the probability that impairment of the adrenal cortex in the manner here described could precipitate the circulatory collapse that often occurs shortly after the onset of fulminant acute infections. The removal of the adrenals from a normal body is, however, different from a loss of cortical secretion during a period of stress such as that represented by a severe infection. In the latter condition the need for the secretion may be greatly increased, analogous to the increased insulin requirement familiar in diabetics during infection. Indeed, it is said that adrenalectomized animals succumb to acute infections more rapidly than animals with adrenals (6); and Thorn and his co-workers (7) have found that acute infections precipitate crises of adrenal insufficiency in patients with Addison's disease under treatment with hormone, and that the hormone requirement is greatly increased in the presence of acute infection. It has

long been noted that the lipoid of the adrenal cortex commonly becomes depleted during severe infections.

Several investigators (8, 9, 10) have reported finding alterations in the blood chemistry characteristic of adrenal insufficiency (decreased sodium and chloride, increased potassium, hypoglycaemia, haemoconcentration) in cases of severe acute infections, and have suggested that the circulatory collapse that occurs in severe infections is due to adrenal insufficiency; and there have been a number of reports of the successful use of adrenal cortical extract and sodium chloride in combatting circulatory failure in infections (8, 11, 12, 13, 16), though not all have had similar success (14, 15). Engelhard (14, lit.), whose efforts were unsuccessful in reducing the mortality in cases of maligant diphtheria, suggested that the great variability in the potency of commercial cortical extracts might be responsible for the conflicting results. Certainly, further studies with standardized material should be carried out. The suggestion presented here that the adrenal cortical damage described in this paper may be related to the circulatory collapse that occurs in some instances of severe acute infections, can at present be regarded as no more than a suggestion which must wait upon further suitable clinical studies for a proper evaluation. It seems nevertheless worthwhile to direct attention to the fact that the adrenal cortex is often severely damaged in this manner in the absence of haemorrhage, not only in cases of meningococcal infection exhibiting the Waterhouse-Friederichsen clinical syndrome, but also in various other severe acute infections in which circulatory collapse is familiar. The zona fasiculata appears to be quite vulnerable to the products of a variety of bacteria. It should be emphasized that even when the lesion here described has not yet developed into its full-blown form, a careful study of the adrenals in these infections commonly reveals numerous isolated necrotic cells in the zona fasiculata; and it is reasonable to believe that still other cells, which are not yet dead, may be functionally damaged.

In order to determine whether the lesion here described might be a *result* of circulatory collapse, the adrenals from nine cases of fatal surgical and traumatic shock were studied. The duration of shock before death was 48 hours in two cases (Autopsy Nos. 9584 and 16708); 24 hours in one case (No. 16166); and from 3 to 20 hours in six cases

(Nos. 15615, 16296, 16526, 16562, 17858, 18554). In none of these cases was the adrenal lesion present. In one case (No. 17858), in which a patient with mitral stenosis died after 20 hours of surgical shock, during which time there had been a mismatched blood transfusion, the cells of the cortical cords were disorganized and in many places separated from each other, as though torn apart postmortem. While simulating the lesion under discussion, the condition of these adrenals was different in numerous respects. That circulatory failure is not necessary for the production of the lesion under discussion is evident from the fact that we have encountered it in focal areas in the adrenals in numerous cases of severe infection in the absence of circulatory failure other than that which occurs terminally in all deaths. Autopsy No. 15226 is a case in point. This was a patient with meningococcal meningitis who died suddenly from oedema of the glottis and pulmonary oedema. The clinical note records that an examination just before this terminal event showed that there was "no drop in blood pressure (180,110). No signs of shock." In the adrenals the lesion under consideration was present in small focal areas.

It is not intended to imply that this adrenal lesion is the sole cause of circulatory collapse in severe acute infections. Doubtless, cardiac rather than peripheral circulatory failure is an important factor in some cases; and in others the bacterial products may cause circulatory failure independently of any effect upon the adrenals. The effects of severe infections upon the cardiovascular system are by no means clearly understood at present. However, in view of the now recognized importance of the adrenal cortex in the maintenance of blood pressure, it seems probable that the extraordinary cortical lesion here described may, if it is not altogether responsible, be at least a contributory factor in some of the instances of circulatory collapse that occur during severe acute infections.

SUMMARY

Various acute infections produce damage to the adrenal cortex, leading to necrosis of isolated cells, and to a striking transformation of the solid cords of the zona fasiculata into tubular structures containing an inflammatory exudate.

The possible relation of this adrenal cortical damage to the circulatory collapse that occurs in some of the patients who suffer from these infections is suggested.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Miss Dorothy Schmitt)

FIG. 1. Normal adrenal cortex, showing the solid cords of lipoid-containing cells.

FIGS. 2 AND 3. Adrenal cortex in case of meningococcal meningitis with circulatory collapse, described in text (Autopsy 18205).

FIG. 4. Adrenal cortex in case of meningococcal meningitis in 8 year old child who died 48 hours after onset of symptoms (Autopsy 17836).

FIG. 5. Adrenal cortex in case of meningococcal meningitis with circulatory collapse, described in text (Autopsy 14853).

FIG. 6. Adrenal cortex in case of meningococcal meningitis with circulatory collapse, described in text (Autopsy 15068).

FIG. 7. Adrenal cortex in case of post-abortion beta-haemolytic streptococcal infection, with clinical history of "state of shock" (Autopsy 10013).

FIG. 8. Adrenal cortex in case of Type III lobar pneumonia with clinical history of "peripheral vasomotor collapse" (Autopsy 16628).

FIG. 9. Adrenal cortex in case of diphtheria (Autopsy 16735).

FIG. 10. Two freshly dead marginal cortical cells, with pyknotic nuclei and coagulated cytoplasm. Same case as Fig. 2.

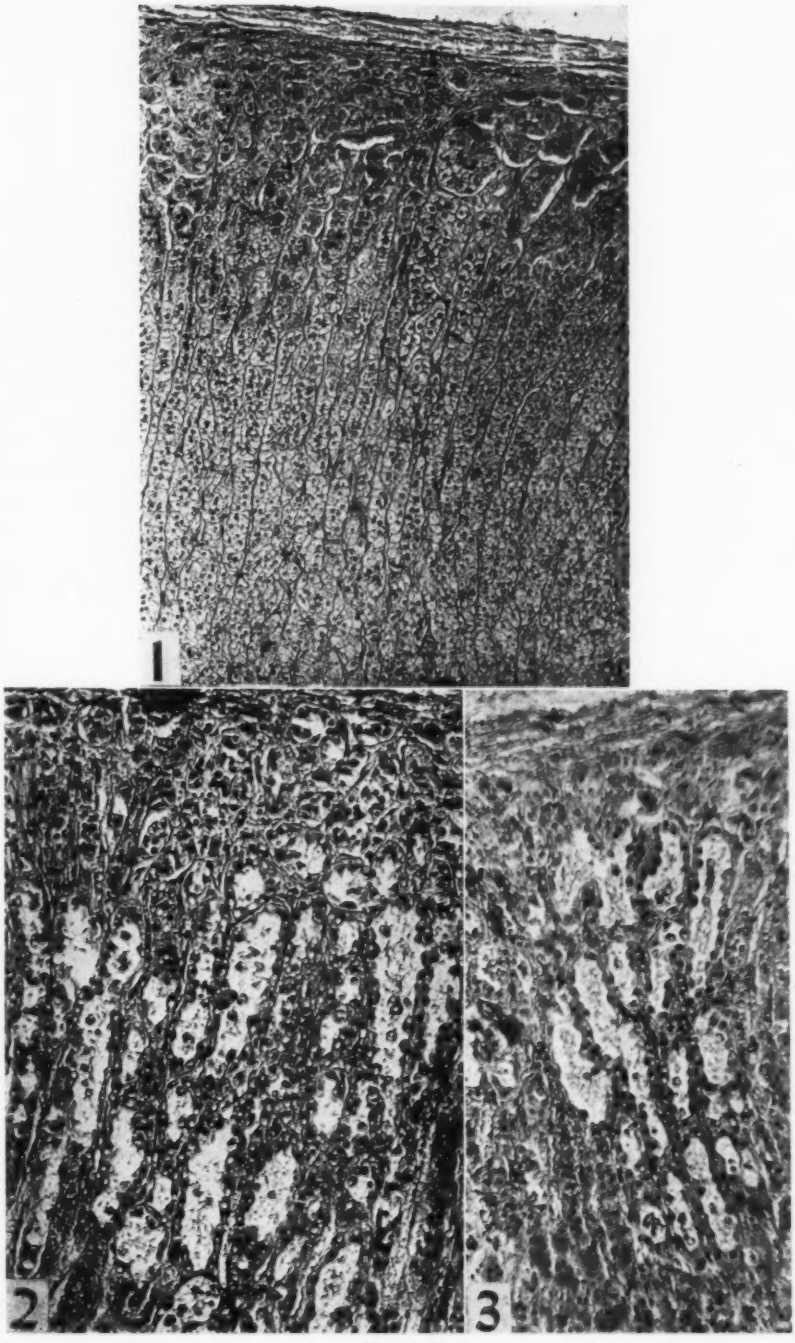
FIG. 11. Dead, partly liquefied marginal cell, leaving a gap adjacent to the capillary which is marked by dotted lines, and from which an exudate of fibrin and several leucocytes has escaped. Same case as Fig. 2.

FIG. 12. Loss of adrenal cortical cell, leaving a gap adjacent to capillary (outlined with dots) from which fluid has escaped into cortical cell column, with beginning separation of cells. Same case as Fig. 2.

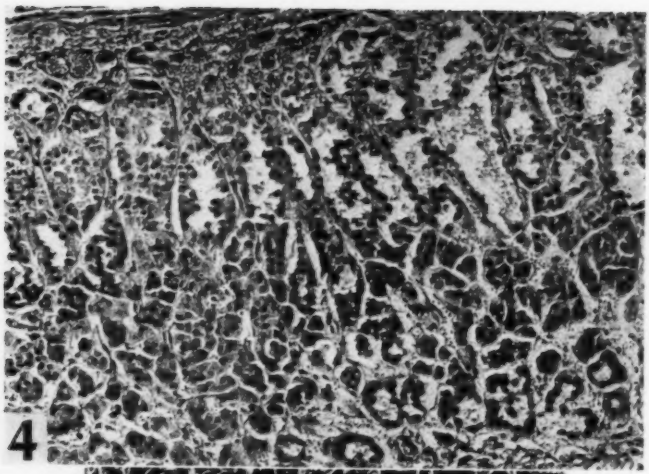
FIG. 13. Leucocytes and fibrin in "tubule" formed in adrenal cortex. Same case as Fig. 2.

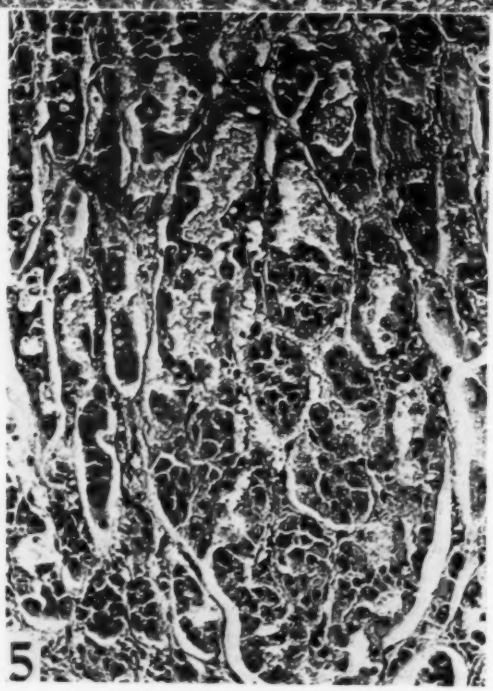
FIG. 14. Fibrin and several leucocytes in "tubule" formed in adrenal cortex. Loss of cells on left side of "tubule". Same case as Fig. 5.

FIG. 15. Fibrin and coagulated protein in "tubule" formed in adrenal cortex. Fibrin radiates from capillary (outlined with dots) adjacent to a gap produced by loss of marginal cells. Same case as Fig. 5.

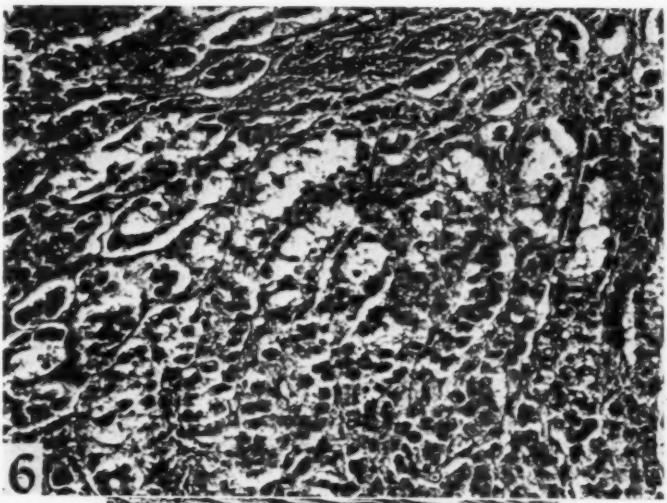


FIGS. 1–3

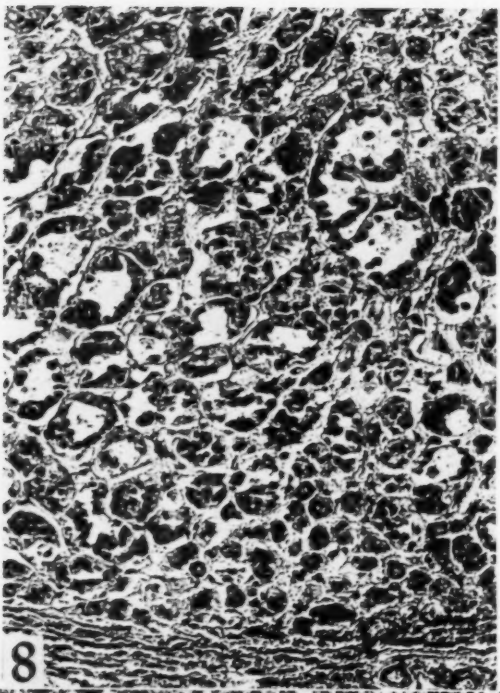


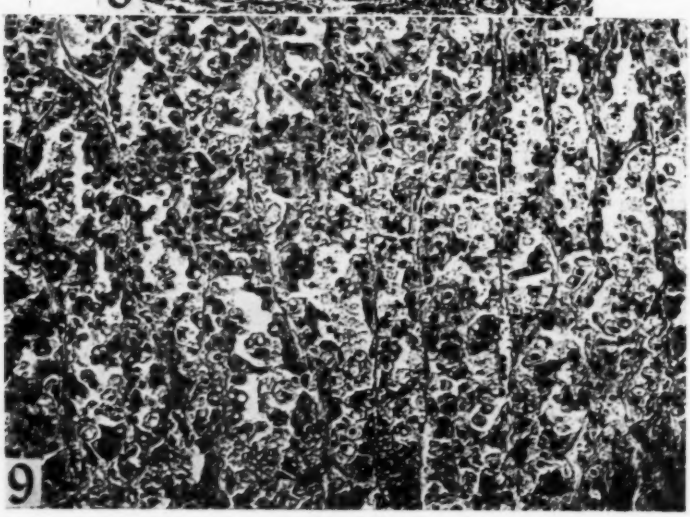


FIGS. 4–5

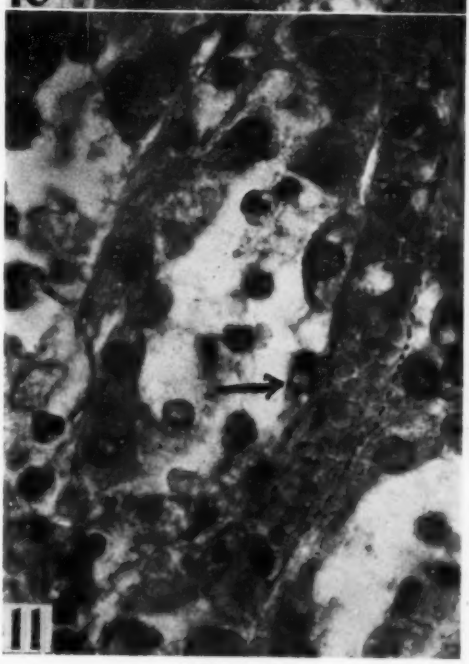


FIGS. 6–7

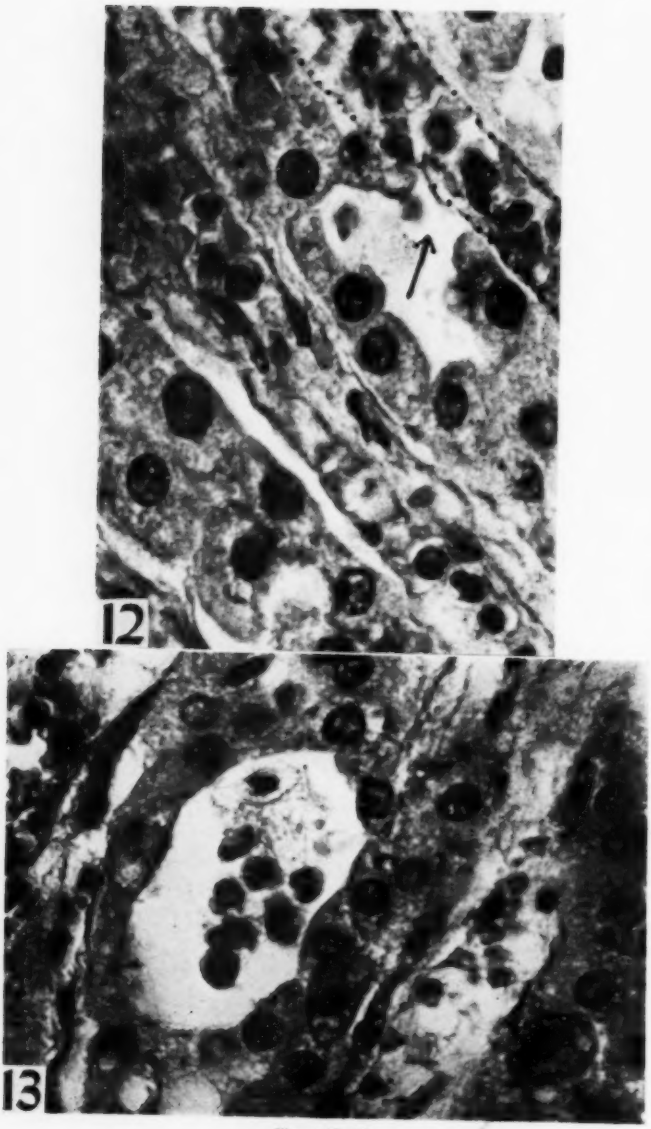




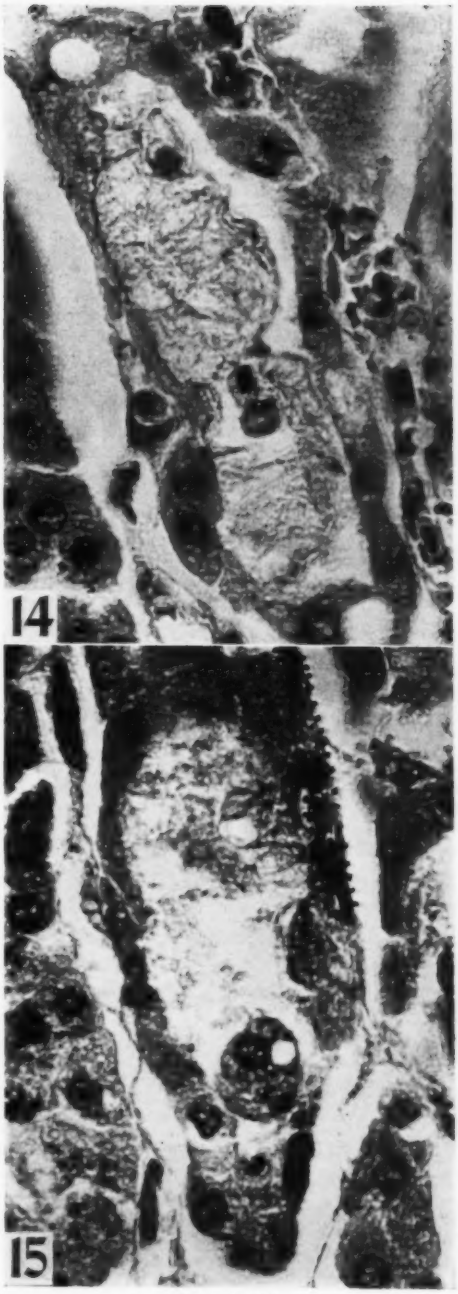
FIGS. 8–9



FIGS. 10–11



FIGS. 12–13



FIGS. 14–15

SUDDEN DEATH IN YOUNG ADULTS IN ASSOCIATION WITH FATTY LIVER

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The purpose of this paper is to call attention to a form of sudden death about which little has been written and little is known. This form of sudden death is one occurring in relatively young adults in whom, at autopsy, no significant pathological lesion is found, except a large, diffusely fatty liver. Almost invariably a history of chronic alcoholism is obtained but (and this should be emphasized) the history supported by chemical analysis, shows also that at the time of death the individuals usually had not been drinking. Death in the typical cases usually results with extreme rapidity and with little or no warning. A total of eleven cases, all occurring within the past year, are reported. Five of these, regarded as the best examples of this type of death, are given in some detail and form the basis of this paper. In these, the sole pathological lesion found at post-mortem examination was a diffusely fatty liver. Six other similar cases are briefly abstracted. In each of these, however, some additional lesion was present at autopsy which might be regarded as the cause or a main contributing cause of death. This article offers no adequate explanation of the mechanism of death, nor does it imply that all persons with such a liver condition die suddenly or unexpectedly. It does maintain that in the cases to be cited, the one common finding of a diffusely fatty liver in association with a sudden and unexpected death is more than would be expected as a coincidence. Clinical and experimental observations to support this are given below.

During the past year I have had the occasion to investigate a number of sudden deaths. The causes of death in the majority of these have been fairly easily determined. In the course of numerous autopsies performed at the Baltimore City Morgue one very striking statistical fact became apparent. This was the high percentage of fatty or cirrhotic livers (or both) found at routine autopsy examination. In many

of these cases some other lesion was found which was responsible for death. In many, too, death was not necessarily sudden. In the ones now being reported, however, death was sudden and unexpected; and the only pathological lesion found at post-mortem examination was a large fatty liver. The first such case to be encountered was extremely baffling and led to a search of text-books and literature on the subject. In only one general text-book of pathology (1) was reference made to the association of sudden death and fatty liver. In several recent articles on the subject of sudden death (2, 3, 4, 5) no mention of this condition is made as a possible cause. Although up to the present time an exhaustive study of the literature has not been made, only a few scattered references relating to the subject have been found.

In 1926 LeCount and Singer (6) called attention to sudden death in association with fatty livers. They reported ten such cases. They give brief abstracts of but two of them. In both there was a history of chronic alcoholism. In both, too, unfortunately, there were autopsy findings which could be interpreted as indicative of heart failure. In one case there was hypertrophy of the heart and in the other slight edema of the ankles. In their other eight cases jaundice was present in six and bronchopneumonia in a large but unstated number. It is of interest, however, that the authors at this time suggested that death might well have resulted from hypoglycemia. They based this belief on the fact that a liver which is completely infiltrated with fat would be unable to store a sufficient amount of glycogen.

In 1934 Judd, Kepler and Rynearson (7) reported two cases of spontaneous hypoglycemia in association with marked fatty infiltration of the liver, confirmed by biopsy. In neither case did the patient die, but in both there were numerous spells of coma and in one actual epileptic seizures. The authors were unable to rule out the possibility of a pancreatic lesion or malfunction but gave evidence to support the view that the fatty condition of the liver was responsible for the clinical picture.

In 1941 Brown and Harvey (8) reported a series of six cases in which severe coma and bizarre neurologic symptoms were found in chronic "smoke" (a form of denatured alcohol) drinkers. During the period of coma, these patients were all found to have severe hypoglycemia. The remarkable thing about these cases was the dramatic response produced

by intravenous administration of glucose. In 1942 Tucker and Porter (9) reported a similar series of cases. In the latter series of cases it is interesting to note that the symptoms of coma, etc., occurred approximately ten to twelve hours after the cessation of drinking and usually following a period of sleep. In 1942 Kalinowsky (10) reported the occurrence of epileptic seizures in two non-epileptic chronic alcoholics. In each of these there had been no history of epilepsy prior to alcohol addiction. In both cases epileptic seizures were noted on several occasions following withdrawal from alcohol.

Experimentally fatty livers have been produced in a number of ways. Paradoxically enough, two of the commonest methods, exclusive of the use of toxic substances, have been by means of starvation diets and by high fat diets. Using the latter method, Best and Huntsman (11) in 1932 first demonstrated the action of choline (choline chloride) in preventing the accumulation of liver fat in white rats. Later experiments by the same authors (12) showed that choline-free diets resulted in a great increase in liver fat. It was further shown that choline was equally effective in removing excessive liver fat despite a continuance of a high fat diet.

Equally interesting experimental work has been recently done with dogs. In 1928 Goldberger and others (13) observed fatty livers in dogs which had been placed on a black tongue producing diet. The following year Sebrell (14) reported the occurrence of sudden death in these dogs. Continuing the investigation Sebrell, Onstott, and Hunt in 1937 (15) showed that dogs put on a riboflavin deficient diet developed "a symptom-complex characterized by sudden collapse and coma, promptly followed by death, unless treated early and with adequate doses of riboflavin." At autopsy no cause of death could be found. In all of the dogs a yellow fatty liver was present. In 1938 Sebrell and Onstott (16) reported a similar work with essentially the same results. Of three dogs dying in this experiment, two were described as having degenerative changes in the central nervous system as well as fatty livers.

The following five cases were all observed within the past year. Three of the autopsies were performed by the writer; the other two were performed by associates, and one of these was witnessed.

Case No. 1. A 34 year old white married female.

History. There was a history of severe chronic alcoholism over a period of at least eight years. According to the deceased's husband, a government engineer, the woman recently had complained of periods of weakness and mild anorexia. Actual quantity of intake of alcohol was not known but was of daily occurrence. The past history, as obtained from the husband and family doctor, was otherwise non-contributory. The night prior to death the deceased complained of not feeling well and ate very little. The following morning, while entering the bathroom at about 8.30 a.m., she was seen to collapse suddenly. By the time a doctor arrived, approximately a half hour later, the woman was dead.

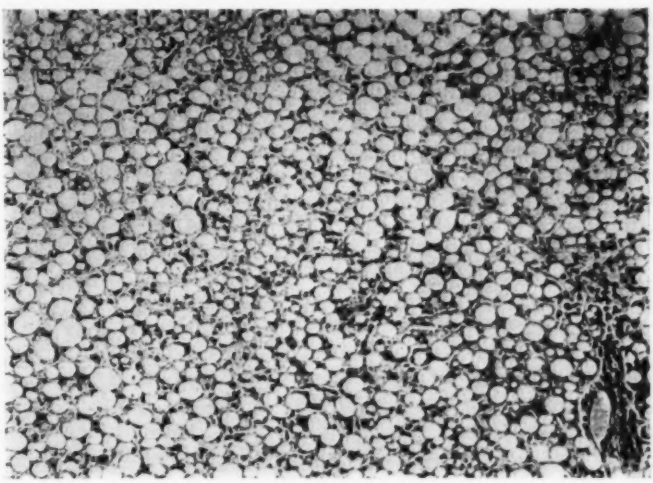

FIG. 1

Autopsy Findings. Height 5'1"; weight 122 lbs. *External Appearance:* the body is that of a well-nourished, well-developed, white female. Except for a tiny abrasion of the skin over the right temple and a few tiny bruises of the lower extremities, there are no marks of injury or violence. *Internal Appearance:* the skull, meninges and brain show no gross lesions. The hypophysis is normal. *Neck Organs and Thoracic Cavity:* there is no obstruction in the mouth or respiratory passages. The lungs are air-containing and soft. A calcified hilar node is present. The heart weighs 265 gms. The heart shows no hypertrophy or dilatation. The valves appear competent. The coronary arteries are delicate. The myocardium is normal. *Aorta:* the aorta is delicate. *Abdominal Cavity:* the liver weighs 2650 gms. It is large and heavy and has a diffusely yellow, fatty appearance. On

section it has a pasty consistency. *Kidneys:* weigh 150 gms. each. The surfaces are smooth. On section they show a purplish congestion, but the markings are clear. *Stomach:* contains one to two ounces of watery, slightly bile-stained fluid. The mucosa has a diffusely pink, slightly hyperemic appearance. The other organs are carefully examined and no lesions are seen.

Microscopic. No lesions are seen except in the liver. This has an extraordinary appearance (fig. 1). Practically every cell is distended with fat globules which in many cases compress the nuclei. There is no cirrhosis.

Laboratory Data. Liver alcohol 0.009%; blood alcohol 0.06%

Blood sugar 4 hrs. post-mortem { (Left auricle): 153.7 mgm. % (Right auricle): 148.3 mgm. %

Case No. 2. A 32 year old white married male.

History. The deceased was a pianist for a visiting orchestra. There was a story of severe alcoholism over a period of three or four years. According to the story, the deceased was attempting to break the habit. Three weeks before death, a spell resembling epilepsy occurred. Other than this the past history was negative. The night prior to death the deceased may have had a few drinks but was definitely known not to have been intoxicated. At about 10 a.m. the day of death he complained that he had been unable to sleep since 7.30 a.m. and was not feeling well. Five minutes later he was heard to collapse on the floor of his hotel room. An associate is an adjoining room found him lying unconscious or dead on the floor, alongside his bed. A lighted cigarette had fallen from his lips. A physician arrived within twenty minutes or so and pronounced the man dead.

Autopsy Findings. Height 5′7″; weight 138 lbs. *External Appearance:* The body is that of a well-developed, moderately well-nourished white male. There are no marks of injury or violence except for a tiny "tooth mark" abrasion of the lower lip.

Internal Examination: The head, including the brain, and the neck organs show no gross lesions. The lungs are air-containing and soft. The heart is entirely normal on gross examination. It weighs 330 gms. The coronaries are examined with extreme care and are delicate. The abdominal organs are grossly normal, except for the liver. The latter weighs 2350 gms. The capsule is smooth. It has a diffusely yellow, fatty appearance. On section the same appearance is maintained. The stomach is empty. The mucosa is slightly hyperemic.

Microscopic: The organs show no lesions except for the liver. This shows marked fatty infiltration involving the greater portion of each lobule.

Laboratory Data: Brain alcohol .03%.

Case No. 3. A 40 year old white unmarried male.

History. The deceased was a newspaper man who, until the day of death, was said to have had normal health. No history of alcoholism, other than social drinking, was obtained from the family. Information from other sources contradicted this. The day of death the deceased spent being examined by physicians

prior to induction in the Army. Approximately three hours after arriving at the examining board, he had a convulsion which was described as epileptic. He was allowed to rest for perhaps two hours and at his request the physical examination was continued. A second convulsive seizure followed. Again he was allowed to rest, and at about 6 p.m. he walked to a waiting Army truck. At this time he did not complain of feeling ill. While being driven home he had a third seizure and died, apparently within a matter of minutes. Examination earlier in the day by Army physicians had revealed no abnormality. The blood pressure was said to have been a trifle elevated at one reading (140/85). No blood chemical studies were recorded.

Autopsy Findings. External Appearance: The body is that of a fairly well-nourished, normally-developed white male of approximately average weight and size. Except for two tiny linear abrasions of the right forehead, the external examination is entirely negative.

Internal Examination: Two small contusions of the scalp are present, but there is no fracture of the skull. The meninges show slight patchy thickening in the parietal lobe on each side. The brain and hypophysis show no gross lesions. *Thoracic Cavity:* the neck organs are not remarkable. The lungs are soft and air-containing. There is slight congestion. The heart is normal in size. There is no evidence of dilatation. The coronary arteries and aorta show only early atheromatous streaking. *Abdominal Cavity:* the liver weighs 3040 gms. The liver has a diffusely fatty appearance. It has a rather orange color. On section the consistency is pasty. *Stomach:* a small amount of watery fluid is present. Tiny punctate hemorrhages are present in the mucosa of the lesser curvature. The rest of the organs, except for congestion, are entirely normal.

Microscopic: One block of brain shows the area of slightly thickened meninges. There is no evidence of any fresh inflammation. The liver shows extraordinary infiltration with fat. The other organs show nothing remarkable.

Laboratory Data: Brain alcohol .011%

Case No. 4. A 27 year old white female.

History. No adequate past history was obtainable about this person, except for the fact of extreme chronic alcoholism. The day of death the deceased was found in a comatose condition on the street. She was admitted to a large general hospital and kept under observation for three hours. At the end of this time, she was discharged since she appeared to have recovered sufficiently. Several hours later in the day she had a second fainting spell and was again admitted to the same hospital. At this time she was comatose and soon went into a condition resembling shock. No blood sugar was taken. She died within two hours.

Autopsy Findings. Height 5′1″; weight 122 lbs. *External Appearance:* The body is that of a well-nourished, well-developed young female. A number of minor old and recent bruises are present over the extremities. A small abrasion of the left knee-cap is present.

Internal Examination: Examination of the head shows nothing remarkable,

except for slightly increased fluid about the brain. The heart and lungs show no gross lesions. Liver weighs 4000 gms. Grossly the liver is swollen and the capsule is tense. On section it has a yellow, diffusely fatty appearance. The stomach is empty. The mucosa is slightly reddened. The other organs, including the pelvic organs, show nothing of significance.

Laboratory Data: Liver alcohol .016%.

Microscopic: Only blocks from the liver were taken at autopsy. These show diffuse fatty infiltration of the liver cells involving practically the entire lobule.

Case No. 5. A 38 year old white male.

History. In this case no definite history of alcoholism could be obtained. The man managed a grocery store. He lived in the same house with a brother-in-law, a doctor. According to the history as obtained, it was the usual custom of the deceased to go out two or three nights a week, frequently remaining out until after midnight. The night prior to death he had returned about 2 a.m. apparently in good health. He was found the next morning dead in bed about 10 a.m. He was pronounced dead by the brother-in-law who could give no adequate cause for death, other than suffocation. He was lying face down in bed but slept without a pillow. Rigor mortis was fully developed.

Autopsy Findings: Height 5'9"; weight 215 lbs. *External Appearance:* The body is that of an obese but normally-developed white male. Livor mortis of the face and neck is marked.

Internal Appearance: Examination of the brain and meninges shows no lesions. The mouth and neck organs are carefully examined for any obstruction or for evidence of external violence. *Thoracic Cavity:* the lungs are somewhat congested but are air-containing. The heart weighs 410 gms. It is distended with partially-clotted blood. Considering the man's size, the heart is little, if any, hypertrophied. The aorta and coronaries are carefully examined and show only early atherosclerotic streaking. The abdominal cavity is essentially negative with the exception of the liver. The liver weighs 2680 gms. It has a congested appearance which, to some extent, obscures the fat infiltration. There is moderate autolysis. The stomach is filled with only slightly digested food material.

Microscopic: The liver shows considerable fat infiltration throughout. A moderate amount of autolysis is present.

Laboratory Data: Blood alcohol .006%. Post-mortem chemical examination for barbiturates, alkaloids, cocaine and strychnine group, arsenic and mercury is negative.

Six other cases of a similar nature have been autopsied within the past year by the author. These were not included in the above series because in each there existed some other pathological lesion at autopsy in addition to an enlarged, fatty liver. In five of the six a definite history of alcoholism was obtained. Four of the cases showed a vari-

able amount of terminal aspiration pneumonia. This condition is undoubtedly common in a number of chronic alcoholics. In two of the cases there was an early hemorrhagic pancreatitis. Only one of the six was intoxicated at the time of death. In the opinion of the author none of these conditions was considered more than a contributory cause of death.

COMMENT

An analysis of the first five cases shows that three were males and two females. All were white. The age ranged from 27 to 40 years, with an average age of 34.2 years. The occupations were not considered of any significance. The economic and social status was considered somewhat above average. None of these cases occurred during the summer season. Of the entire eleven cases none occurred between the period of late June and late September.[1] This fact is of value, if only to rule out the possibility (unfortunately not a rarity in Baltimore) of heat stroke or heat exhaustion.

The past history of the first five cases was singularly negative, except for alcoholism. This was definitely present in three and thought to be present in four. The post-mortem chemical examinations of tissues reported above all gave values for alcohol too low to be compatible with acute alcoholism at the time of death. As to clinical symptoms, three had attacks of unconsciousness prior to death and in two of these the attacks were described as epileptic, or convulsive. One had vague symptoms of weakness and anorexia for several months prior to death. In three of the cases death was known to have occurred within a half hour or less from the time of collapse. In one, death occurred during sleep, and in the fifth there was a two or three hour period of coma preceding it. The appearance at autopsy examination of all five was strikingly uniform, namely the absence of any gross lesions except for the liver. Microscopic examination showed a similar uniformity. In three of the cases no normal liver cells could be found, although several blocks were taken. Each liver cell was variably distended with a fat

[1] It seems worth recording that the incidence of fatty livers in the autopsy series at the Baltimore City Morgue is considerably lower during the summer months than during the rest of the year.

globule. In some the globules of fat were so large as to compress the nuclei into a crescent shape. In the other two cases, the picture was only slightly less marked.

The number of these cases are too few and the clinical and laboratory data are too incomplete to give a clear-cut picture of this type of death. Perhaps the most striking feature is the apparent lack of specific clinical signs or symptoms. One case (No. 3) was under the observation of a group of physicians for almost the entire day of his death. He was not considered to be acutely or seriously ill. A second case (No. 4) was discharged from a hospital the day of death for the same reason. The diagnosis, therefore, in this type of case is obviously difficult. Indeed, it is doubted whether present-day liver function tests would have shown any abnormality.

A second striking feature is the suddenness of death. Four of these cases closely simulated a coronary death; yet the most careful search showed no demonstrable heart lesion. The cases associated with convulsive seizures might conceivably be compared to another so-called liver death, namely eclampsia. What relation, if any, there might exist between the two is unknown.

In conclusion it is of course obvious that the mechanism of death is not known. The clinical evidence cited would suggest spontaneous hypoglycemia as the cause. Unfortunately, only one post-mortem blood sugar was obtained and this was not lowered. The experimental work with dogs suggests a vitamin deficiency. This latter hypothesis is supported by the known inadequacy of the diet of alcoholics. Further studies will be made in an attempt to shed more light on this condition.

SUMMARY

1. Attention is called to the occurrence of sudden death in young adults in association with marked fat infiltration of the liver.

2. Five such cases occurring within the past year are cited and mention is made of 6 other cases.

3. No known reason for the cause of death has been ascertained, but it is suggested that a vitamin deficient state, with or without hypoglycemia, might be responsible.

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AN INTRADERMAL TEST FOR THE RECOGNITION OF HYPERSENSITIVITY TO THE SULFONAMIDE DRUGS

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The tendency of the sulfonamide drugs to produce hypersensitive reactions and at times cause permanent sensitivity to these compounds in many patients must be constantly borne in mind whenever the use of one of these important chemotherapeutic agents is contemplated. At times these reactions are almost indistinguishable from a complication of the original disease or from a new infectious process. Since clinical recognition of drug reactions is frequently difficult, and failure of recognition may result in serious damage to the patient, it was hoped that a simple, reliable diagnostic aid might be found to demonstrate drug sensitivity. The present investigation suggests that an intradermal test, using human serum from patients receiving sulfonamide orally, might be useful. Long (1) has recently estimated that between 10 and 15 million people received one of the sulfonamide derivatives last year, and warns of the danger of sensitizing a large section of our population. Should this occur the urgent need and value of such a test is apparent.

Among the common clinical manifestations of sensitivity to the sulfonamides are fever, dermatitis, and conjunctivitis. Reports of the incidence of such hypersensitive phenomena vary from 2 to 36 percent (2–12). Sulfanilamide, sulfapyridine, and sulfadiazine seem to be the offenders with about the same frequency (4), (11), (13), while sulfathiazole is quite definitely more prone to produce sensitization than the others (4), (11), (13). The astounding occurrence of a febrile reaction in 36 percent of 53 patients receiving a second course of sulfathiazole reported by Lyons and Balberor (9) is not corroborated by other investigators. In a study of 964 patients who had received sulfathiazole, selected at random from the Johns Hopkins Hospital records, Nelson (12) found the incidence of a febrile or cutaneous toxic reaction to be 11.2% during the first administration of the drug, with approximately the same incidence (10.4% of 133 patients) on second administration in those patients who showed no reaction with the first course of therapy.

There is much clinical evidence that hypersensitivity to the sulfonnamides is a true allergic reaction, very similar to serum sickness. Hageman and Blake (2) first drew attention to the similarity of sulfanilamide reactions and serum sickness. Rich (14) calls attention to the similarity of the urticarial and other forms of "drug rash," to the rash seen with serum sickness. Chills and fever, conjunctival injection, myalgia and arthralgia, eosinophilia, angioneurotic edema, and bronchial asthma have all been reported with sulfonamide reactions, (2, 9, 13, 15, 16, 17, 18, 19, 20, 31). The hypersensitive nature of periarteritis nodosa has recently been demonstrated by Rich (14, 39) in patients who had hypersensitive reactions to foreign serum or to sulfonamides, and Rich and Gregory (40) have produced the lesion experimentally in animals subjected to serum sickness. In the human cases of periarteritis nodosa associated with sulfonamide hypersensitivity that were reported by Rich there were also present widespread visceral, focal inflammatory-necrotic lesions of the character described by Lederer and Rosenblatt (15), and by Merkel and Crawford (21) in patients dying after sulfathiazole medication. That hypersensitivity plays an important part in the fatal reactions from the sulfonamide drugs is shown by an analysis of the instances of death due solely to these agents in New York City in 1941 summarized by Sutliff and his associates (22). Of the 28 fatal cases, drug fever or rash preceded other signs of drug toxicity in 9, and were present at some time in 14, while either dermatitis or hyperpyrexia or both were the only signs of toxicity in 4 cases. Additional evidence for the allergic nature of sulfonamide sensitivity is the response seen to very small doses of drug, and the long duration of the hyper-reactive state. Erskine (20) has reported a case in which 0.5 gms. of sulfapyridine given twelve months after the original sensitization caused edema of the larynx. Cohen and his associates (23) tell of a woman who was sensitized by the local application of sulfathiazole to the skin and three weeks later the ingestion of 8 mgm. of sulfathiazole produced a generalized papuloerythematous eruption. Gallagher (24) has observed a febrile response to the administration of sulfanilamide two years after the first course of therapy, during which no reaction had been seen.

Most attempts to demonstrate sensitivity to the sulfonamides by means of skin tests have failed (2, 9, 18, 23, 25, 26, 27, 28, 29, 30).

In two patients who developed a rash during oral sulfanilamide therapy, Goodman and Levy (29) performed scratch, patch, and intradermal tests using sulfanilamide as the powder and in solution. In one of these patients all three tests were negative, while in the other patient the scratch test was positive, though the intradermal and patch tests were negative. Salvin (31) obtained a positive patch test in a patient who developed angioneurotic edema and urticaria from sulfanilamide. More recently others (19, 32) have reported positive patch tests in individuals sensitized by the topical application of sulfathiazole. Kalz and Steeves (19) found the patch tests positive using sulfanilamide, sulfapyridine, sulfadiazine, and sulfathiazole powder, though the patient had been exposed previously to sulfathiazole alone. On the other hand Weiner (32) tested two of his cases of sensitization to sulfathiazole with the other drugs and obtained negative results, while patch tests with sulfathiazole and sodium sulfathiazole were positive. Passive transfer studies (9) and attempts to demonstrate serum precipitins (13, 28, 30, 33, 34) have been negative. However, Wedum (28, 35) has recently succeeded in sensitizing animals to sulfanilamide, sulfathiazole, and sulfapyridine azoproteins, made by conjugation with egg white, beef serum, and human serum by the Landsteiner technic. He was able to demonstrate anaphylaxis, positive intradermal tests, and precipitins in these animals, using the homologous chemoprotein.

The present investigation is a study of 76 patients seen at Johns Hopkins Hospital, from March to July, 1943, 38 of whom were thought by other observers to be clinically hypersensitive to various sulfonamide drugs, and 38 of whom were not thought hypersensitive and served as controls. Eight of those thought to be hypersensitive were found on close study to fulfill incompletely the criteria for definite drug sensitivity, and will be referred to as "Questionably hypersensitive." The requirements for inclusion of a patient in the "Definitely hypersensitive" group were:

1. The occurrence of a rash, fever, or conjunctivitis in the course of sulfonamide therapy that was not related to the original disease or due to a secondary process.
2. Complete and permanent disappearance of the above signs upon cessation of the sulfonamide drug.
3. A time interval between the beginning of sulfonamide medication and the appearance of hypersensitive phenomena of at least 6

days, unless a history of previous administration of the drug was established.

The ability of the sulfonamides to combine with the plasma proteins has been clearly demonstrated by Schönholzer (36) and Davis (37). Rich (14) suggests that, attached to the plasma proteins, they may act as haptens and in this way sensitize the body specifically. Thinking along these lines it seems reasonable to suppose that there might be present in the circulating blood of an individual receiving a sulfonamide therapeutically, with an effective blood level, an antigenic substance capable of causing sensitization in some instances, and possibly able to produce an allergic skin reaction when the serum of such an individual is injected intradermally in a person who is hypersensitive to the homologous sulfonamide. Before this approach to the problem was tried simpler substances were used in performing intracutaneous tests on 4 patients who were known to be definitely hypersensitive to sulfathiazole. Sodium sulfathiazole 100 mgm.% in normal saline, sodium sulfathiazole 100 mgm.% in normal human serum incubated for 24 hours at 37°C., acetyl sulfathiazole in normal saline, and acetyl sulfathiazole incubated with human serum were used with completely negative results. Blood was then drawn from a patient who had been receiving sulfathiazole, 3 grams a day, for 7 days, with a level of 4 mgm.% of free sulfathiazole. This serum was injected intradermally into the 4 sulfathiazole sensitive patients with the production of a typical allergic wheal in each case.

More than 300 intradermal tests have been performed on the 76 patients studied, using 40 different samples of serum as the testing agents. Each of the sera used contained one of the following sulfonamides: namely, sulfanilamide, sulfathiazole, sulfadiazine, and sulfamerazine (sulfamethyldiazine). These sera were obtained from patients suffering from some acute bacterial infection who had been treated with one or another of the drugs, whose blood cultures were negative, and in whom the serologic test for syphilis was negative. Twenty to thirty cubic centimeters of blood were drawn from the antecubital vein under sterile precautions and placed in a sterile centrifuge tube and allowed to clot. The clot was separated from the container with a sterile glass rod, and the tube centrifuged at high speed for twenty minutes. The serum was pipetted off and placed in sterile, rubber stoppered containers, 0.5 cc. being added to Brewer's medium

and incubated for 72 hours as a check for sterility. The various sera were obtained from patients who had been receiving sulfonamide either by mouth or by the parenteral route for periods of from 1 to 15 days, with drug levels of 2 to 20 mgm.%, in order to determine the influence of these factors on the antigenicity of the serum. In order to control the test, each patient was bled either before the administration of sulfonamide or during convalescence when the serum was completely free of the drug.

The intradermal test required the use of tuberculin syringes and 26 gauge needles. Into the flexor surface of the forearm 0.05 cc. of the control serum and 0.05 cc. of each of the sulfonamide sera were injected intracutaneously, the tests being placed above the controls. The size of the wheal and the diameter of the erythema were then measured immediately after injection, and at intervals of 5 minutes for 20 minutes. The initial wheal size was found to be 6 or 7 mm. in diameter. In the negative tests and in control subjects the size of the wheals increased only 1 or 2 mm. (up to 7 or 8 mm. in diameter), and the slight redness that appeared was pale in color and covered only a small area (up to 20 mm. in diameter). This corresponds fairly well to the reactions described by Chant and Gay (38) when heterologous human sera were injected intradermally, though they used double the amount (0.10 cc.) that was used in the present investigation. Positive tests observed in patients definitely hypersensitive to one of the sulfonamides showed an immediate increase in the size of the homologous wheal up to 12 to 18 mm. in diameter, with intense erythema 30 to 40 mm. in diameter, and the development of pseudopods when the reaction was marked. This became maximal in 15 minutes after the injection and was fading in 30 minutes, so that by the end of an hour and a half all traces of the wheal were gone. Inspection of the sites of injection at 24 and 48 hours revealed no instance of a delayed reaction. A difference between the size of the control wheal and the size of the test wheal of at least 4 mm. diameter was used as a criterion for positivity, rather than absolute size of the test wheal.

Table I is a summary of the pertinent clinical and experimental data in each of the 76 cases studied. It is interesting that of the 30 definitely hypersensitive patients 18 were sensitive to sulfathiazole alone, 3 to sulfanilamide alone, 2 to sulfadiazine alone, and 4 to sulfamerazine.

The three other patients were each sensitive to more than one drug, clinically—one to sulfapyridine and sulfathiazole, one to sulfanilamide and sulfathiazole, and one to sulfadiazine and sulfathiazole. Thus there was a total of 21 patients sensitive to sulfathiazole, 4 to sulfanilamide, 3 to sulfadiazine, 1 to sulfapyridine, and 4 to sulfamerazine. During the time interval covered by the study (March through June, 1943) sulfathiazole was used in this hospital in an amount approximately 3 times that of each of the other sulfonamides except sulfapyridine, which was used to a negligible extent. Sulfadiazine, sulfanilamide, and sulfamerazine were used in about equal quantities The fact that sulfathiazole sensitivity was seen 7 times as frequently as sulfadiazine, and 5 times as frequently as sulfanilamide and sulfamerazine corroborates the view that sulfathiazole is the most dangerous of the sulfonamides in this respect. This may be the result of the tendency to sulfathiazole to become bound to plasma albumen in greater proportion than the others, as was shown in the experiments of Davis (37).

It will be noted that 3 cases (nos. 13, 15, and 72) showed a positive reaction to the serum control. Each of these gave a typical allergic response, with a large wheal and pseudopods, to the normal human serum, yet did not give such a response to the test sera containing in vivo protein bound sulfonamide. In each instance the serum was not fresh, but had been kept at ice-box temperature for a period of at least 30 days. Case 15 is especially instructive because this individual was tested with samples of the same sulfathiazole serum and the same control on two occasions, at an interval of 27 days, both sera being kept in the ice-box in the meantime. On the date of the first testing both skin reactions were negative, while on the second occasion the sulfonamide skin reaction remained negative, but the control serum produced an allergic response. In these cases aging at ice-box temperature did not cause the sulfonamide serum to elicit false positive tests. The tendency of normal, control human serum to produce a marked reaction after aging in the ice-box confirms the observations of Chant and Gay (38), who observed the same phenomenon in skin testing human subjects with their own serum.

Table II summarizes the skin reactions observed in 64 patients who had received one of the sulfonamides therapeutically, using as a testing

TABLE I

Clinical and experimental data

CASE NO.	AGE SEX	CLINICAL DIAGNOSIS	HISTORY OF ALLERGY	HISTORY OF PREVIOUS SULFONAMIDE ADMINISTRATION	HYPERSENSITIVE REACTION TO SULFONAMIDE	DESCRIPTION OF HYPERSENSITIVE REACTION		DATE OF SKIN TEST (1943 IN EACH)	TIME INTERVAL BETWEEN HYPERSENSITIVE REACTION AND SKIN TEST	INTRADERMAL TEST (SULFONAMIDE SERUM = SERUM CONTAINING IN VIVO PROTEIN BOUND SULFONAMIDE)								
						Definite	Questionable			Sulfathiazole serum	Sulfadiazine serum	Sulfanilamide serum	Sulfamerazine serum	Na sulfathiazole 100 mgm.% in NaCl	Na sulfathiazole 100 mgm.% + serum	Acetyl sulfathiazole in NaCl	Acetyl sulfathiazole serum +	Control serum
(1) W. L. staff	26 M	well	0	Sulfadiazine throat spray for 2 days, Nov. 1942	none noted			3/13 4/1		0 0	0		0	 0				0 0
(2) W. N. staff	22 F	acne	0	Sulfathiazole ointment to skin daily for one year, 1942	note noted			3/13 3/20		0 0	0							0 0
(3) M. S. med.	62 F	cystitis	0	Sulfathiazole, 3 gms. daily from 3/1–3/10/43	+	Temp. normal until 3/10 then fever of 105°, which disappeared after drug was stopped		3/13 3/18	3 days 8 days	+ +	0				0			0 0
(4) A. G. staff	26 M	well	asthma	0				3/15		0								0
(5) M. M. med.	35 M	pneumonia	0	Sulfapyridine, 6 gm. a day from 2/27 to 3/8/43 3/17—sulfathazole, 4 gm. at 4:00 p.m. and 1 gm. at 8:00 p.m.	+	Fever to 104°, erythematous rash, on 3/8/43 No fever after 3/9 until 3/17, then rash and fever up to 104°, at 9 p.m.		3/15 3/19	7 days 2 days	0 +	0 0							0 0
(6) M. J. med.	40 M	broncho-pneumonia	0	Sulfapyridine, 6 gms. daily from 2/14 to 2/16/43 Sulfathiazole 6 gms. daily 3/7 to 3/8/43	+	Erythematous, papular rash on hands on 3/8/43 disappeared when drug stopped		3/15	7 days	+	0							0
(7) E. K.	20	parturition	0	Sulfathiazole, 6 gms.	+	No fever until 10/26, then		3/15	4½ mos.	+	0							+

		nia		2/16/43 Sulfathiazole 6 gms. daily 3/7 to 3/8/43		disappeared when drug stopped														
(7) E. K. med.	20 F	parturition	0	Sulfathiazole, 6 gms. daily from 10/17 to 10/22/42 Then sulfathiazole 7 gms. from 10/26 to 10/28/42	+	No fever until 10/26, then temp. of 106° for 3 days, with macular rash. Stuporous from 11/7 to 11/26/42. Residual neurological damage present still		3/15	4½ mos.	+	0								+
(8) M. T. urol.	65 M	prostatectomy	0	Sulfathiazole, 3 gms. q.d. from 3/7 to 3/17/43, and 10 gms. on 3/18/43	+	No fever until 3/18/43 then rash & temp. of 105°		3/19 3/30	1 day 12 days	+ +	0 0			0	0				0 0
(9) R. C. urol.	15 M	urethritis	0	Sulfathiazole, 3 gms. q.d. from 3/6 to 3/18/43	+	Temp. normal until 3/18, then fever of 104°. Generalized rash		3/19	1 day	+	0								0
(10) B. T. urol.	35 M	epididymitis	0	Sulfathiazole, 4 gm. q.d. from 3/4 to 3/14/43	+	Fever up to 104° and rash on 3/14, lasted 48 hrs.		3/19	5 days	+	0								0
(11) M. H. staff	25 F	well	0	Sulfadiazine throat spray in October, 1942	none noted			3/19		0	0								0
(12) E. P. med.	47 F	erysipelas	0	Had sulfathiazole before admission, then sulfanilamide, 1 gm. q. 6 hr. from 3/14 to 3/20/43	+	3/20, generalized rash, (maculo-papular), disappeared when drug stopped		3/21	1 day	0	0	+	0	0	0				0
(13) M. C. staff	25 F	well	0	Sulfanilamide for 1 wk. in 1940	none noted			3/22		0		0		0					+
(14) R. T. staff	29 F	well	0	Sulfathiazole for sore throat on 3 occasions in 1941-42	none noted			3/22		0	0			0					0
(15) C. T. surg.	24 M	sinusitis	0	No sulfonamide until 5/10-5/12/43 then sulfathiazole 4 gms. q. day	?+		After 4 gms. of drug on 5/11, urticarial rash, which persisted five days	5/12 6/8	1 day 28 days	0 0	 0								0 +
(16) K. B. staff	28 F	well	0	Sulfanilamide for 3 weeks, in large doses in 1938	+	Three episodes of fever and rash, and anemia, in 1938 when on drug		3/24 4/2 4/2	5 yrs. 5 yrs. 5 yrs.	 0 0	0	+ 0 +	(rt. arm) (rt. arm) (left arm)						0 0 0
(17) T. H. staff	30 M	well	0	Sulfadiazine throat spray in 1942	none noted			3/24				0							0

TABLE I—*Continued*

CASE NO.	AGE SEX	CLINICAL DIAGNOSIS	HISTORY OF ALLERGY	HISTORY OF PREVIOUS SULFONAMIDE ADMINISTRATION	HYPERSENSITIVE REACTION TO SULFONAMIDE	DESCRIPTION OF HYPERSENSITIVE REACTION		DATE OF SKIN TEST (1943 IN EACH)	TIME INTERVAL BETWEEN HYPERSENSITIVE REACTION AND SKIN TEST	INTRADERMAL TEST (SULFONAMIDE SERUM = SERUM CONTAINING IN VIVO PROTEIN BOUND SULFONAMIDE)								
						Definite	Questionable			Sulfathiazole serum	Sulfadiazine serum	Sulfanilamide serum	Sulfamerazine serum	Na sulfathiazole 100 mgm.% in NaCl	Na sulfathiazole 100 mgm.% + serum	Acetyl sulfathiazole in NaCl	Acetyl sulfathiazole + serum	Control serum
(18) B. C. med.	20 F	drug reaction? cellulitis	0	3/14/43 sulfathiazole 1 gm. then 3 gms. daily for 4 days, 3/20–21, sulfathiazole 15 gms.	+	3/20, swelling of neck, thought to be cellulitis, also erythema nodosum, both disappeared when sulfathiazole stopped		3/27 4/2 4/2	1 wk. 2 wks. 2 wks.	+ + +				0 0	0 0			0 0 0
(19) M. F. ophth.	25 F	ophthalmitis, traumatic	0	Sulfathiazole 4 gms. q.d. 3/24 to 3/28/43, sulfadiazine 6 gms. on 3/29	?+		3/28, killed typhoid bacilli, intravenously and temp. to 103°, lasted 3 days, also transient erythema	3/29	1 day	0	0				0			0
(20) R. B. ophth.	45 M	glaucoma	0	Post operatively, sulfadiazine 6 gms. q.d. 3/21–23, 1943	none noted			3/29		0	0							0
(21) R. K. ophth.	54 F	cataract	0	Sulfathiazole 3 gms. on 3/28/43	none noted			3/29		0								0
(22) W. K. surg.	25 M	fracture of femur	0	Sulfathiazole for G.C. before admission, postoperatively 3/25/43 sulfathiazole 7 gms.	?+		3/25, fever 104°, fell on stopping drug, but on two occasions in next week fever went to 103° without drug	3/29	4 days	0		0						0

(23) W. J. surg.	46 M	gastric resection	0	Sulfathiazole, 4 gm. daily from 3/17 to 3/22/43. Sulfadiazine 6 gms. daily 3/30–4/5/43	none noted			3/29 3/30		+ +	0								0 0
(24) O. J. med.	21 M	meningitis	0	Sulfamerazine 4 gm. stat, and 1 gm. q. 8 h. 3/20–3/20/43	?+		3/23, macular rash accompanying meningitis became more marked	3/29	6 days				0						0
(25) L. R. ophth.	52 F	cataract		Post-operatively sulfathiazole 4 gms. daily, 3/9–3/15/43	+	3/16, erythema nodosum, disappeared when drug stopped		3/30 4/7	2 wks. 3 wks.	+ +	0	+	0		+	0	0		0 0
(26) J. H. med.	70 M	cystitis	0	Sulfathiazole 2 gms. q. day, 3/24–3/31/43	+	No fever until 3/31, then temp. of 105°		4/1	1 day	0					0				0
(27) B. A. med.	65 M	pneumonia	0	Sulfathiazole 3 gms. q. day, 3/25–3/31/43	?+		3/31, papular eruption of left hand, conjunctivitis of left eye only	4/1	1 day	0					0				0
(28) B. Y. student	23 M	well	hay fever	0					4/3		0			0					0
(29) M. N.	29 F	hemolytic anemia	0	Sulfanilamide 6 gm. 3/30/43 Sulfathiazole 6 gm. 4/1/43, jaundice and hemolytic anemia on 3/31	none noted			4/3		0		0							0
(30) M. B. urol.	64 M	prostatectomy	0	Sulfathiazole 3 gms. q.d. from 3/18 to 3/28/43	+	No fever until 3/28, then temp. of 103°, fell to normal when drug stopped		3/30	2 days	+				0	0				0
(31) B. H. ophthal.	65 F	cataract	0	Sulfathiazole 3 gm. q.d. from 3/29 to 4/5/43	+	No fever until 4/5, then temp. of 104°		4/7	2 days	+							0	0	0
(32) S. H. med.	38 M	pneumonia	0	Sulfamerazine 4 gm. stat, 1 gm. q. 8 hrs. 4/4 to 4/9/43	none noted			4/19		0		0	0						0

TABLE I—*Continued*

CASE NO.	AGE SEX	CLINICAL DIAGNOSIS	HISTORY OF ALLERGY	HISTORY OF PREVIOUS SULFONAMIDE ADMINISTRATION	HYPERSENSITIVE REACTION TO SULFONAMIDE	DESCRIPTION OF HYPERSENSITIVE REACTION		DATE OF SKIN TEST (1943 IN EACH)	TIME INTERVAL BETWEEN HYPERSENSITIVE REACTION AND SKIN TEST	INTRADERMAL TEST (SULFONAMIDE SERUM = SERUM CONTAINING IN VIVO PROTEIN BOUND SULFONAMIDE)								
						Definite	Questionable			Sulfathiazole serum	Sulfadiazine serum	Sulfanilamide serum	Sulfamerazine serum	Na sulfathiazole 100 mgm.% in NaCl	Na sulfathiazole 100 mgm.% + serum	Acetyl sulfathiazole in NaCl	Acetyl sulfathiazole + serum	Control serum
(33) M. W. staff	35 M	well	0	Sulfathiazole ointment for 1 week in September, 1942	+	Erythematous, macular rash over area of application of the ointment		4/8	7 mos.	+							0	0
(34) M. A. med.	18 F	urticaria	+	0				4/5			0	0						0
(35) M. G. med.	40 F	arsenic intoxication	0	Sulfathiazole 1 gm. t.i.d. 3/7 to 4/3/43	none noted			4/5		0	0							0
(36) M. D. med.	45 F	erythema elevatum diutinium	0	Sulfanilamide 0.5 gm. q. 4 hrs. for 4 days in 1940, and again at same dose in Sept. 1941 for 4 days	+	Nausea, vomiting, and fever of 104° with the second administration in 1941		4/5	1½ yrs.		0	+						0
(37) W. L. staff	60 M	well	0	Sulfadiazine thr. spray and by mouth occasionally in 1941 and 1942. Sulfathiazole ointment to hand March 27–28, 1943	none noted			4/5		0	0							0
(38) R. D. staff	25 M	well	occas. hives	0				4/17		0	0	0				0	0	0

(39) W. M. med.	99 M	Hodgkin's disease	0	0				4/9		0							0	0
(40) R. C. med.	19 M	pneumonia	0	Sulfathiazole 0.5 gm. q. 4 hrs. for 1 week in Sept. 1942, then 0.5 gm. q.d. for next 2 months	+	Generalized urticarial rash and fever to 103° at end of 1st week of treatment		4/9 4/17	6 mos. 6 mos.	+ +							0	0 0
(41) L. B. med.	45 M	rheumatoid arthritis	0	Sulfanilamide 6 gms. a day Aug. 1–7, 1940, and May 1–3, 1941 Sulfadiazine 3 gms. q. day, Mar. '43 Sulfanilamide nasal spray Apr. 8, '43	+	Aug., 1940, morbilliform rash. May, 1941, rash & fever. April 8, '43, Hemorrhagic rash on hands		4/9 4/12 4/19	3½ yrs. after first reaction	+ +	0	+ +	0 0					0 0 0
(42) G. C. staff	25 M	well	0	0				4/20		0	0	0						0
(43) M. H. staff	25 M	well	0	0				4/20		0	0	0						0
(44) J. G. staff	27 F	well	sens. to horse serum	0				4/20		0	0	0						0
(45) W. J. ped.	4 F	otitis	0	Sulfathiazole nose drops 1/25 to 1/30/43. Then by mouth, 1½ gms. stat, and ½ gm. q. 4 hrs. 4/10–4/11/43	+	4/11/43, erythematous rash on chest and abdomen, followed by desquamation		4/25	2 wks.	+	0		0					0
(46) V. R. staff	23 F	well	0	0				4/26		0	0	0	0					0
(47) M. K. med.	56 F	pneumonia	0	Sulfathiazole 15 gms. 4/20/43 then 1 gm. q. 6 hrs. 4/24–29/43	none noted			4/26		0	0	0	0					0

TABLE I—*Continued*

CASE NO.	AGE SEX	CLINICAL DIAGNOSIS	HISTORY OF ALLERGY	HISTORY OF PREVIOUS SULFONAMIDE ADMINISTRATION	HYPERSENSITIVE REACTION TO SULFONAMIDE	DESCRIPTION OF HYPERSENSITIVE REACTION		DATE OF SKIN TEST (1943 IN EACH)	TIME INTERVAL BETWEEN HYPERSENSITIVE REACTION AND SKIN TEST	INTRADERMAL TEST (SULFONAMIDE SERUM = SERUM CONTAINING IN VIVO PROTEIN BOUND SULFONAMIDE)								
						Definite	Questionable			Sulfathiazole serum	Sulfadiazine serum	Sulfanilamide serum	Sulfamerazine serum	Na sulfathiazole 100 mgm.% in NaCl	Na sulfathiazole 100 mgm.% + serum	Acetyl sulfathiazole in NaCl	Acetyl sulfathiazole + serum	Control serum
(48) B. G. ophth.	6 F	conjunctivitis	0	Sulfathiazole 2 gms. q.d. 4/21–4/24/43. Sulfathiazole ointment to eyes 4/24–29/43	?+		4/24/43, generalized macular rash, which disappeared while pat. was getting the ointment	4/27	3 days	0			0					0
(49) J. H. ped.	8 mos. M	tracheo-esophageal fistula	0	Sulfathiazole 0.25 gm. q. 6 hr. 9/7–14/42. Sulfadiazine, 0.25 gm. q. 6 h. 9/13–16/42. Sulfathiazole 1 gm. q.d. 4/9–18/43, then sulfadiazine 1 gm. q.d. 4/23–25/43	+	9/14/42, rash on legs after sulfathiazole (no rash after 2nd course of sulfathiazole in 1943). 4/25/43, generalized rash (after 2nd course of sulfadiazine)		4/27	2 days	0	+							0
(50) E. N. staff	29 M	well	sensitive to Iodine	0				5/5			0		0					0
(51) M. B. med.	29 M	pyelonephritis	0	Sulfathiazole 6 gms. q.d. for 4 weeks between Feb. and May, 1943 Sulfanilamide 1 gm. May 2, 1943	none noted			5/2		0	0	0	0					0

				Sulfamerazine 4 gms. q.d.	+	5/4, erythematous macu-		5/5	1 day		0		+					0

				May 2, 1943															
(52) J. M. med.	52 M	pneumonia	0	Sulfamerazine 4 gms. q.d. from 4/26/43 to 5/4/43	+	5/4, erythematous maculo-papular rash, and fever to 102°		5/5	1 day		0		+					0
(53) A. B. med.	36 F	lung abscess	0	Sulfadiazine 6 gms. q.d. from 8/27/42 to 9/3/42.	+	9/3/43, erythematous macular rash		5/5	8 mos.		+		+					0
(54) L. N. urol.	23 M	gonorrhea	0	Sulfadiazine, 6 gms. q.d. 3/15 to 4/1/43, and 4/7–21/43. Sulfathiazole 2 gm. on 5/1/43. Sulfanilamide 4 gm. q.d. 5/4–13/43	+	4/21/43 erythema nodosum, fever 103° conjunctivitis. 5/1/43, generalized erythematous rash		4/22 5/15	1 day 25 days	+ +	0 +	0						0 0
(55) D. S. staff	22 F	well	0	Sulfathiazole nose drops for 2 days in January, 1943.	none noted			5/12		0	0		0					0
(56) M. R. med.	40 F	check-up	0	Sulfadiazine 6 gm. q.d. 9/11–12/43 and 3/24–25/43. Sulfanilamide, 2 gms. q.d. 10/6–7/42.	none noted			5/13		0	0							0
(57) D. C. student	23 M	sinusitis	sens. to horse serum	Sulfathiazole, 4 gm. q.d. for 1 wk. in Dec. 1940. Sulfathiazole powder as nasal spray 5/3/43	+	5/3/43, 2 hrs. after spray, generalized urticarial rash		5/13	10 days	+								0
(58) M. B. med.	27 F	meningitis	0	Sulfathiazole 6 gm. q.d. 4/24–28, 1943. Sulfamerazine 6 gm. q.d. 4/29–5/7/43, then 3 gm. on 5/12	+	5/7/43, fever to 103° fell when drug stopped. 5/12, fever of 102°		5/14	1 wk.	0			+					0
(59) J. R. ped.	2 mos. M	pneumonia	0	Sulfathiazole 0.9 gm. q.d. 5/3–5/8/43.	none noted			5/14		0								0
(60) W. H. med.	52 M	pneumonia	0	Sulfamerazine 4 gm. stat, and 4 gm. q.d. 4/16–26/43, and same dosage 5/9–12/43	+	No fever until drug resumed on 5/9, then temp. of 105°, remained up until drug stopped on 5/12		5/21	12 days				+					0

TABLE I—*Continued*

CASE NO.	AGE SEX	CLINICAL DIAGNOSIS	HISTORY OF ALLERGY	HISTORY OF PREVIOUS SULFONAMIDE ADMINISTRATION	HYPERSENSITIVE REACTION TO SULFONAMIDE	DESCRIPTION OF HYPERSENSITIVE REACTION		DATE OF SKIN TEST (1943 IN EACH)	TIME INTERVAL BETWEEN HYPERSENSITIVE REACTION AND SKIN TEST	INTRADERMAL TEST (SULFONAMIDE SERUM = SERUM CONTAINING IN VIVO PROTEIN BOUND SULFONAMIDE)								
						Definite	Questionable			Sulfathiazole serum	Sulfadiazine serum	Sulfanilamide serum	Sulfamerazine serum	Na sulfathiazole 100 mgm.% in NaCl	Na sulfathiazole 100 mgm.% + serum	Acetyl sulfathiazole in NaCl	Acetyl sulfathiazole + serum	Control serum
(61) R. C. med.	29 M	pneumonia	0	Sulfamerazine 4 gm. stat, and 3 gms. daily 5/6–15/43	none noted			5/21					0					0
(62) E. W. med.	48 M	pneumonia	0	Sulfamerazine 4 gm. stat, and 3 gms. q.d. 5/10–5/19/43	none noted			5/21					0					0
(63) J. J. med.	29 M	pneumonia	0	Sulfamerazine 4 gm. q.d., 5/14 to 5/19/43	none noted			5/21					0					0
(64) L. D. med.	29 F	pneumonia	0	Sulfathiazole 6 gm. q.d. 4/30 to 5/17/43	none noted			5/23		0			0					0
(65) K. S. med.	37 F	pneumonia	0	Sulfamerazine 4 gm. stat, and 3 gms. q.d. 5/7–5/15/43	none noted			5/23			0		+					0
(66) B. Y. med.	36 F	pneumonia	urticaria	Sulfamerazine 3 gm. q.d. May 13 to May 15, 1943	?+		Slight scaling of hands before drug. Then on May 13, '43 rash became generalized, papulo-vesicular	5/23	10 days		0		+					0
(67) B. M. urol.	28 M	nephrectomy	0	Sulfathiazole, 4 gm. q.d. 5/8 to 5/11/43, then 3 gm. q.d. 5/13 to 5/16/43	+	No fever until 5/15, then temp. 105°, erythema of face		5/23	8 days	+	0		0						0

				gm. q.d. 5/13 to 5/16/43		of face														
(68) M. N. student	23 M	bronchitis	0	Sulfadiazine thr. spray q. 2 hrs. for 5 days in Dec., 1942, again thr. spray from 4/7–4/12/43	?+		4/12/43, erythema multiforme, conjunctivitis, gge, splenomegaly and temp. of 102°	4/17 5/18	5 days 1 mo.	 0	0 0								0 0
(69) R. H. med.	16 M	regional ileitis	0	Sulfathiazole 4 gm. q.d. from 4/2 to 4/18/43	+	4/14, erythema nodosum, and conjunctivitis, which disappeared when drug stopped		4/28 5/2	10 days 2 wks.	0 0	0 0	 0							0 0
(70) P. H. student	24 F	well	fam. hist.	0				6/7					+						0
(71) R. B. med.	22 M	scarlet fever	0	Sulfamerazine 4 gm. q.d. from 5/28 to 6/6/43	+	6/7/43, morbilliform rash, conjunctivitis, eosinophilia of 10%		6/7	8 hrs.				+						0
(72) E. D. med.	25 F	P.U.O.	0	Unidentified sulfonamide drug 4 gm. q.d. 4/20 to 4/28/43	none noted			6/8		0	0								+
(73) C. T. med.	40 M	chronic ulcer of leg	sens. to adhesive	Sulfathiazole ointment to leg, 2/15 to 5/20/43. Sulfathiazole orally, 6 gm. q.d. 5/20–30/43	+	5/20/43, urticarial rash fever, spiking type to 104°, edema of eyelids, eosinophilia 17%		6/17	4 wks.	+									0
(74) E. W. med.	35 M	urticaria	+	Sulfathiazole cream to skin, 6/1–6/8/43	none noted			6/17		0	0								0
(75) D. B. ped.	6 M	rheum. fever	0	Sulfathiazole 0.5 gm. q. 4 hrs. 6/15–6/19/43, developed jaundice	none noted			6/26		0									0
(76) J. M. ped.	6 mo.	otitis hepatitis due to Sulfadiazine		Sulfadiazine grains ii, 5 times a day from 6/16–6/18/43 Sulfathiazole, grains ii ss. 6/18	none noted			6/28		0	0								0

agent the homologous sulfonamide serum. Of the 30 definitely hypersensitive patients, positive skin tests were obtained in 28; thus the skin test was found to be reliable in more than 90% of the hypersensitive individuals studied. The test was positive in only 1 of the 8 persons who were thought clinically to be questionably sensitive. Among the group of 26 patients[1] in whom no hypersensitive phenomena were observed clinically 24 gave negative skin tests and 2 showed positive skin reactions. Both of these individuals had received the sulfonamide drug longer than 6 days, so that they may have become sub-clinically

FIG. 1. A TYPICAL POSITIVE REACTION

(Case No. 57, 5-13-43.) The upper reaction occurred ten minutes after the injection of sulfathiazole serum. The lower reaction occurred at the same interval of time after the injection of control serum.

sensitized, and the skin tests in this case do not necessarily represent false positive reactions.

Intradermal tests were performed on 50 patients with a different sulfonamide than that which they had received therapeutically, or to which they had had clinical hypersensitive reactions. The results of these tests, which are tabulated in Table III, show no positive skin reactions in the groups which were questionably hypersensitive or had no observed sensitivity phenomena. Only 3 of the 25 definitely hypersensitive patients tested in this way were found to give positive skin

[1] There were actually in this study 27 persons who had received a sulfonamide without observed sensitivity. One of these was not tested for the same sulfonamide he had ingested, but was tested for others. This patient is included in Table III.

tests to sulfonamides other than the offending drug. This shows that the skin test is relatively specific for the individual sulfonamide drugs, since this incidence corresponds closely to the frequency of clinically

TABLE II

Skin Tests Made with the Same Sulfonamide that Was Used in the Treatment of Each Patient

PRESENCE OR ABSENCE OF CLINICAL REACTION FOLLOWING ADMINISTRATION OF THE DRUG	POSITIVE SKIN TEST	NEGATIVE SKIN TEST	TOTAL
Clinical reactions present	28	2	30
Clinical reactions questionable	1	7	8
Clinical reactions absent	2	24	26
Total	31	33	64

TABLE III

Skin Tests Made with a Different Sulfonamide than That Used in the Treatment of Each Patient

CLINICAL REACTION TO GENERAL ADMINISTRATION	POSITIVE SKIN TEST	NEGATIVE SKIN TEST	TOTAL
Definite hypersensitivity	3	22	25
Questionable hypersensitivity	0	6	6
No observed hypersensitivity	0	19	19
Total	3	47	50

TABLE IV

Skin Reactions Observed in 11 Individuals Who Had Never Received a Sulfonamide Drug

FORM OF SULFONAMIDE USED IN THE SKIN TEST	POSITIVE SKIN TEST	NEGATIVE SKIN TEST	TOTAL
Sulfanilamide	0	7	7
Sulfathiazole	0	9	9
Sulfadiazine	0	7	7
Sulfamerazine	1	4	5
Total	1	27	28

observed sensitivity to other sulfonamides than the one which has acted as a sensitizing agent.

Table IV shows the skin reactions encountered in 11 individuals who had never received a sulfonamide drug in any form. In these people

28 skin tests were performed with various sulfonamides, 27 of which were negative while 1 positive test was observed in an individual whose family history revealed allergy in some form, hay fever, asthma, or urticaria, in every member of the family, although the patient herself had never had any allergic disease. It cannot be decided whether this allergic predisposition was the cause of the false positive skin reaction.

The sulfonamide serum used in skin testing may possibly contain the antigen responsible for the sensitization of some individuals during sulfonamide administration. In some respects its behavior is like an antigen, but this is not true of all of its properties. Various studies were made with interesting, though confusing results. Its high degree of specificity has already been referred to. Freezing, and preserving the serum in a frozen state for 2 months had no effect on its ability to evoke positive skin tests, nor did keeping it at ice-box temperature change it in this respect or cause it to produce false positive reactions. Heating the material at 60°C. for 3 minutes caused it to lose its ability to produce a positive skin test performed on an individual sensitive to the same sulfonamide, although an unheated sample of the same serum injected simultaneously in the same person produced a strongly positive test. Various sulfonamide sera and controls were diluted 1 to 2, 1 to 5, 1 to 10, and 1 to 20 with normal saline and injected intradermally into patients known to be sensitive (both clinically and by previous test) to the homologous sulfonamide. At 1 to 2 and 1 to 5 dilutions positive tests were obtained, but beyond that dilution there was no distinguishable difference between the test and the control wheals.

In order to determine how closely the sulfonamide is bound to the serum proteins in the testing material the following experiment was carried out on a sample of sulfathiazole serum which was known to have been successful in producing a positive skin test in sulfathiazole sensitive individuals. Two cubic centimeters of this serum, which contained a level of sulfathiazole of 10.2 mgm.% free drug, and a total level of 16.0 mgm.%, were placed in a cellophane bag and sealed tightly. The bag was placed in a flask containine 1500 cc. of 0.85% NaCl through which a current of air was passed continuously to agitate the fluid. Dialysis was allowed to occur for 17 hours, after which the bag was opened and the volume of the serum found to be 2.5 cc. Analysis of the sulfathiazole content of the serum revealed a free level of

0.2 mgm.%, and a total level of 0.4 mgm.%. Calculation of the absolute amounts of sulfathiazole present in the serum gave the following results: Before dialysis in 2 cc. of serum: free drug, 0.204 mgm.; total drug, 0.320 mgm. After dialysis (volume 2.5 cc.): free drug, 0.005 mgm.; total drug, 0.010 mgm. The dialysate was discarded, and the 2.5 cc. of serum, now practically free of sulfathiazole, was sterilized by passing it through a Berkefeld filter. Skin tests done on the same sulfathiazole sensitive patients described above were all negative. Another sample of the same serum was passed through a Berkefeld filter and was found to retain the ability to evoke a positive skin test in sulfathiazole sensitive persons. Thus we see that, if it is a combination of the sulfonamide and plasma protein which gives positive skin reactions, this combination appears to be easily split, separable by dialysis through an appropriate membrane. The small amount of sulfonamide remaining in the serum after dialysis is insufficient to produce an allergic skin response in sensitive patients.

The level of sulfonamide in the test serum seemed to be relatively unimportant in respect to the ability of the serum to produce positive reactions, since sera with free sulfonamide levels varying from 2 to 25 mgm.% were found to be equally successful. It was found however that when the sulfonamide level fell to 1.5 mgm.% or below, positive skin reactions could not be obtained. The amount of acetylated drug in the successful sera varied from 0.5 mgm.% to 6 mgm.%. Serum drawn from patients who had been receiving sulfonamide therapeutically for less than 5 days was uniformly incapable of causing a positive skin test in patients sensitive to the homologous sulfonamide, regardless of drug level.

The time interval between the onset of symptoms of hypersensitivity and the performance of intradermal test was from 8 hours to 5 years. In case # 71 a positive skin test to sulfamerazine was obtained 8 hours after the appearance of a morbilliform rash which occurred on the 7th day of treatment with this drug. In this particular case the intradermal test was of value in deciding whether the picture was due to drug sensitivity or to German measles (especially since there was a case of German measles on the same floor of the hospital at the time). Case # 54 illustrates an important point, because the intradermal test for sensitivity to sulfadiazine was negative 1 day after the clinical

picture of drug allergy developed, while 25 days later the skin test was positive for sulfadiazine and sulfathiazole. (In the meantime he had received 2 gms. of sulfathiazole and immediately responded with a generalized erythematous rash.) However, in most instances the skin test was positive almost immediately after signs and symptoms of hypersensitivity appeared.

Several cases were found to give positive skin tests many months after the occurrence of clinical hypersensitivity, and 3 cases (Nos. 16, 36, and 41) were found to be skin test positive for the homologous sulfonamide longer than a year after the drug reaction. The occurrence of an allergic skin reaction to sulfanilamide serum 5 years after the patient had reacted clinically to sulfanilamide with fever and rash (no sulfonamide drug had been administered in the interval) suggests that clinical sensitivity to the sulfonamides may persist for this length of time. The longest period of clinically verified drug sensitivity found in the literature is 2 years (24).

SUMMARY

A method has been described by which positive skin tests may be obtained in patients who have shown hypersensitive reactions to the sulfonamide drugs. The material used for the skin test consisted of serum obtained from patients who were receiving a sulfonamide therapeutically and contained a drug level of from 2 to 25 mgm.%. This skin test is simple to perform, may be easily and quickly interpreted, and was found to be reliable in the diagnosis of drug sensitivity in 28 out of 30 cases of definite drug reactions. It is hoped that this test may be useful, both in the differential diagnosis of drug reactions, and perhaps as a precautionary measure before starting sulfonamide therapy in patients who have previously received one of these compounds. The fact that positive skin tests may be so consistently obtained in sensitive individuals is additional evidence that drug sensitivity is an allergic reaction. The sensitizing antigen may be a sulfonamide plasma protein combination which occurs in vivo in the circulating blood of patients during sulfonamide therapy, the sulfonamide perhaps acting as a haptene. The failure of two patients in this series (Nos. 75 and 76) who developed hepatitis and one patient (No. 29) who developed hemolytic anemia as a result of sulfonamide therapy,

to show positive skin reactions for the homologous sulfonamide, supports the belief that these latter reactions are due to direct toxic action of the sulfonamide rather than to hypersensitivity.

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THE INFLUENCE OF A MONOCYTOSIS OF THE PERIPHERAL BLOOD STREAM UPON THE CELLULAR CHARACTER OF AN ACUTE INFLAMMATION

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As is well known, it is a characteristic of acute inflammation that polymorphonuclear leukocytes predominate over mononuclear cells in the early stages of the development of the exudate. After a lapse of time, varying with the character and intensity of action of the irritant, mononuclears gradually predominate over the polymorphonuclears.

Some years ago, Dienes and Mallory (1), after studying tuberculin reactions in experimental animals, reported that mononuclear phagocytes predominated over polymorphonuclears in the reactions at all times, even in the earliest stages of the reaction. Even with death of tissue, the polymorphonuclear exudation was sharply localized around the necrotic areas and the remainder of the inflammation produced was predominantly mononuclear in character. They believed that the mononuclear character of the tuberculin reaction contrasted so sharply with the predominantly polymorphonuclear picture of anaphylactic reactions that the two types of hypersensitivity reactions could be differentiated by the cellular character of the exudate. Follis (2) repeated painstakingly the procedures of Dienes and Mallory dealing with tuberculin reactions and was unable to confirm their results. Polymorphonuclears always predominated over mononuclears in the early stages of the reactions.

It is true that mononuclear cells tend to appear earlier in greater numbers in tuberculin reactions than in similarly early stages of inflammations produced in normal bodies. It has been suggested by Rich (3) that in the case of tuberculosis and tuberculin reactions this fact might be due not to hypersensitivity, but to the monocytosis which exists in the blood stream during progressive tuberculosis, with correspondingly greater opportunity for such cells to escape at any inflamed site. The monocytosis in experimental tuberculosis is often

marked, 25% to 35% of the total white blood count being frequent and even slightly over 50% having been reported (4).

The present study was undertaken in an attempt to ascertain whether monocytes would occur in increased numbers in a non-hypersensitive, non-specific, acute inflammatory exudate when there is a high level of such cells in the peripheral blood.

METHOD

The monocytosis was produced in albino rabbits by infecting them with B. (Listerella) monocytogenes. While varying in other respects (total white cell count, percentage of polymorphonuclear leucocytes, percentage of lymphocytes, presence and numbers of nucleated red blood cells), the blood in all cases contained a substantial increase in monocytes, well developed by the 72nd hour and maintained for at least 48 hours thereafter. The monocytosis varied from about 25% to about 50% of the total white blood count. During the period in which the monocytes were approximately in the 30% range, three intracutaneous injections were made, each of 0.1 cc. of beef infusion broth, concentrated ten times, in order to stimulate a mild inflammation, since it was emphasized by Dienes and Mallory that the monocytosis of the tuberculin reaction is to be sought particularly in early very mild reactions. The skin was prepared by careful shaving immediately before the injections, in order to avoid making injections into a previously irritated area. In two animals, carefully depilated by barium paste immediately before injection, no histologic differences were noted. Each test animal was controlled by carrying out simultaneous injections of the same amount of the broth concentrate into the skin of a normal rabbit.

The three sites injected were removed at 6, 12 and 24 hours respectively, from both test and control rabbits. White blood counts, differentials, and (in infected animals) blood cultures were made at the period of injection and at each biopsy period. The skin strips were fixed in Zenker-formol (10% formalin), and thin hematoxylin and eosin stained sections were made through the marked center of the site of injection. Bacterial stains were also made on sections from the infected animals. Differential cell counts of the inflammatory exudates were made. Monocytes and polymorphonuclears were counted

TABLE I

RABBIT NO.	BLOOD DIFFERENTIAL COUNTS (% OF PMN AND MONOCYTES ONLY)								LESION DIFFERENTIAL COUNTS (% OF PMN AND MONOCYTES)						BLOOD CULTURES OF TEST ANIMALS FOLLOWING THE INTRACUTANEOUS INJECTION OF BROTH
	0 hr.		6 hr.		12 hr.		24 hr.		6 hr.		12 hr.		24 hr.		
	PMN	Mon.	PMN	Mon.	PMN	Mon.	PMN	Mon.	PMN	Mon.	PMN	Mon.	PMN	Mon.	
X E*	30	36	40	40	37	37	32	36	50	50	59	40	80	20	Positive at injection. Not
80 C	26	2	41	3	59	5	55	5	96	4	95	5	97	3	done later
40 E	37	47	51	38	55	33	44	45	59	41	49	51	51	49	Negative at 0, 6, 12, 24 hrs.
42 C	25	4	35	2	27	3	45	3	87	13	64	36	66	34	
44 E	52	37	44	45	>30	>30	>30	>30	56	44	75	25	66	34	Negative at 0, 6, 12, 24 hrs.
45 C	42	5	66	0	†	Few	†	Few	93	7	76	24	70	30	
50A E	56	31	72	27	68	23	51	38	49	51	65	35	87	13	Positive at 0, 6, 12, 24 hrs.
51A C	57	4	66	1	55	1	55	3	93	7	58	42	58	42	
35 E	†	30	61	16	41	32	59	15	33	67	34	66	61	39	Negative at 0, 6, 12, 24 hrs.
37 C	12	3	32	4	†	†	40	3	85	15	97	3	89	11	
51 E	54	31	51	32	49	37	35	44	54	46	55	45	64	36	Positive at 0 hr.; negative
21 C	57	7	62	7	57	8	76	8	91	9	91	9	90	10	at 6, 12, 24 hrs.
39 E	42	31	†	†	46	31	32	31	50	50	82	18	56	44	Negative at 0, 6, 12, 24 hrs.
51A C	57	4	66	1	55	1	55	3	93	7	58	42	58	42	
41 E	50	38	50	38	60	36	64	32	68	32	62	38	80	20	Negative at 0, 6, 12, 24 hrs.
43 C	51	5	45	2	60	4	44	0	88	12	80	20	85	15	
89 E	41	48	60	31	56	30	54	38	56	44	59	41	56	44	Positive at 0 and 12 hrs.;
91 C	24	4	37	3	52	5	46	5	91	9	92	8	89	11	negative at 6 and 24 hrs.
50 E	50	38	60	30	65	26	56	29	70	30	92	8	60	34	Negative at 0, 6, 12, 24 hrs.
22 C	54	4	57	15	45	7	54	11	93	7	83	17	86	14	

* E indicates test animal, C indicates control animal.

† These smears were unsatisfactory for detailed counts to be made.

in order, omitting doubtful cells. Lymphocytes were not counted, and were very few. One hundred cells were counted in most instances. Two hundred cells were counted in some cases, but no considerable difference was found between the first and second hundreds counted.

In three pairs of animals (40E, 42C; 44E, 45C; 41E, 43C), intracutaneous tests with a concentrated suspension of heat killed B. monocytogenes were carried out, just before the injections of broth, in order to ascertain whether any hypersensitivity had developed, although this was thought to be very unlikely due to the brief period of infection. All such tests were negative at $\frac{1}{4}$ and $\frac{1}{2}$ hour, and at 1, 2, 4, 6, 12, 24, 48 and 72 hours.

RESULTS

The inflammations produced by the broth were for the most part very mild, and in only a few sections was any necrosis of tissue to be seen, this apparently along the needle track.

Usually by fairly careful microscopic examination of the sections from the test and control animals, observers could detect which biopsy was from which animal. When histologic differential counts were made, in ignorance of whether the skin was from an experimental or a control rabbit, the results were very clear, as shown in Table 1. At 6 hours in the controls a high percentage (90% or over, usually) of the exudate cells were polymorphonuclears, the remainder monocytes. In the test animals, the ratio of polymorphonuclears to monocytes was usually about 50–50 at this period. One case showed two-thirds monocytes at 6 hours.

Many pairs of biopsies could be differentiated at 12 and 24 hours, but in many other cases this was not so, and no constant direction of change can be described. Thus, in some test animals, the polymorphonuclears increased at 12 and 24 hours, in some controls the monocytes increased.

The results of the blood cultures are shown in Table 1.

Bacterial stains of the lesions of the test animals failed to reveal any bacteria.

DISCUSSION

Murray, Webb and Swann (5), who discovered and described the bacterium used in the present experiments, used various irritants (peptone broth of questionable sterility, B. coli, B. monocytogenes) to produce a pleural inflammation in normal and monocytogenes-infected

rabbits. They found no difference between test and control animals in the cellular components of the pleural exudates at 6 hours (the only time studied), except when B. monocytogenes was injected into the pleura of an animal having a bloodstream monocytosis. In this situation, a great percentage of the cells in the exudate were monocytes. Since B. coli and peptone broth failed to be associated with mononuclear exudation in the rabbits having bloodstream monocytosis, Murray, Webb and Swann concluded that the attraction of the bacterium for the monocytes was a specific one. It is possible that the discrepancy between their results and those in the present work may be due to the much more intense inflammations produced by the character and quantities of the irritants used by Murray and his coworkers.

Also of interest in connection with this problem are other studies which have appeared dealing with nonspecific, induced inflammations in tuberculous animals. Kaufmann (6) found a higher mononuclear cell percentage in the contents of cantharidin blisters in tuberculous animals than in normals. Dienes and Mallory (1), using intracutaneous turpentine in tuberculous guinea pigs, Laporte (7), using plain broth and glycerine broth in tuberculous guinea pigs, and Lurie (8), using aleuronat in pleurae of tuberculous guinea pigs and rabbits, all found more mononuclear cells in the inflammations induced in tuberculous animals than in normal controls. Of these, only Lurie attempted to correlate the leukocytic formula of the exudate with the blood picture. He was disinclined to believe that any inter-relationship existed. However, in Lurie's differential counts, only 'granulocytes' and 'nongranulocytes' were distinguished, and not 'granulocytes', 'lymphocytes' and 'monocytes'. No conclusion, therefore, can be drawn regarding the relationship of the blood picture to the number of mononuclear phagocytes in the lesions.

Since the present work indicates that the number of monocytes in non-specific inflammatory exudates (at least under the conditions herein employed) is increased incident to increasing the numbers of such cells in the blood, it seems clear that the monocytosis of experimental tuberculosis must be taken into consideration in the interpretation of the augmented monocyte content of the inflammatory exudates in the tuberculous body.

CONCLUSIONS

In the presence of a monocytosis in the peripheral blood, the appearance of appreciable numbers of monocytes in acute inflammatory exudates is accelerated.

Since progressive tuberculosis is accompanied by a monocytosis, often of considerable degree, this fact must be taken into consideration in the interpretation of the earlier appearance of appreciable numbers of monocytes in tuberculin reactions and in nonspecific inflammations in the tuberculous body.

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INFLUENCE OF CERTAIN AMINO ACIDS ON HISTAMINE REACTIONS AND ANAPHYLACTIC REACTIONS IN INTESTINAL STRIPS OF GUINEA PIGS AND IN INTACT GUINEA PIGS

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Experimental inhibition of anaphylactic shock has been the subject of numerous investigations for years. Hill and Martin (1), in 1932, listed and discussed as many as 165 agents which had been used for this purpose up to that time.

Undoubtedly many of the investigators had in mind the ultimate therapeutic usefulness of such inhibiting substances. When, therefore, in 1939 Ackermann and Wasmuth (2) were not only able to confirm the work of Edlbacher, Jucker and Baur (3) (who had inhibited or suppressed the histamine contraction of the intestinal strip of guinea pigs by the amino acids arginine, histidine, and cysteine), but moreover succeeded in inhibiting with arginine the reaction of the intestinal strip of sensitized guinea pigs to serum, they thought of continuing their observations with their eye on a possible therapeutic value of such effects.

Linneweh (4), of the Pediatric Department of the University of Berlin, in the course of an extensive study on alimentary intoxication of infants, reported in 1940 on the work of these authors, and summarized a later paper by Rothlin as follows: 1. The histamine effect is inhibited by arginine not only in the isolated intestine of the guinea pig, but also in the isolated uterus of guinea pigs and rabbits, and in the isolated seminal vesicles of the guinea pig. 2. The effect of acetylcholine on those organs is not influenced by arginine. 3. The adrenalin effect on those organs is not influenced by arginine. 4. The effect of pitocin is inhibited by arginine (though to a lesser extent). Linneweh himself succeeded in repeating the inhibition of the histamine effect and of the antigen effect on intestinal strips of guinea pigs by adding arginine to the Tyrode solution prior to or together with histamine or serum respectively. He then proceeded to the injection of arginine monochloride into the abdominal cavity of guinea pigs

with the aim of preventing anaphylactic shock and histamine shock in the living animal.

Linneweh's results were as follows: 1. Out of 10 guinea pigs of 300 gm. weight which had received 50 gamma histamine intravenously or 100–200 gamma intraabdominally, an average of 8 or 9 died (it seems but it is not specifically stated that several such series were tested). When, however, 1 gm. arginine monochloride had been injected intraabdominally in a group of guinea pigs "corresponding in number and weight", all the animals survived the injection of histamine given 4 to 6 hours later. Their hairs were bristled up, some lost urine and feces, but respiratory symptoms were absent. Some animals died after several hours, "perhaps due to peritoneal irritation produced by the arginine or histamine injection." Histological examinations showed only very slight distention of the alveoli of the lungs in the arginine animals compared with the typical picture in the controls. 2. Out of 10 guinea pigs sensitized subcutaneously with 0.1 cc. wether[1] serum 8 died in anaphylactic shock after 22 days following intravenous injection of 0.2 cc. of the same serum. Those animals, however, who received 1 gm. arginine monochloride intraperitoneally 4 to 6 hours prior to the shocking dose of serum exhibited no shock symptoms; "some minutes after the intravenous injection of the serum the animals were unfastened and were running around lively."

Linneweh felt that his observations gave promise for a desensitizing therapy; yet he was unable to continue his studies due to the fact that arginine was not available.

All these observations reported by the different authors, if proven to be correct, seemed to deserve attention from a theoretical as well as possibly from a practical viewpoint. We undertook therefore to study the problem involved, as soon as we obtained, in the fall of 1941, a supply of arginine monohydrochloride through the courtesy of Merck & Co.

I. ACTION OF ARGININE AND HISTIDINE ON THE HISTAMINE EFFECT AND ON THE ANTIGEN EFFECT IN THE INTESTINAL STRIP OF GUINEA PIGS

2 cc. of lower ileum of a guinea pig were suspended in Tyrode solution (50 cc. Tyrode solution, made up according to Burn (5), was used

[1] Castrated ram.

as bath throughout these studies). Addition of 4 gamma histamine (histamine acid phosphate Lilly) to the bath produced typical contraction. After changing the bath 1 cc. of arginine monohydrochloride in $\frac{1}{2}$ molar solution, neutralized with KOH, was added to the Tyrode solution. Two minutes later 4 gamma histamine were again introduced in the bath and now the muscle failed to respond. A new piece of intestine was then subjected to the action of histamine. After changing the bath 4 gamma histamine were added, but this time

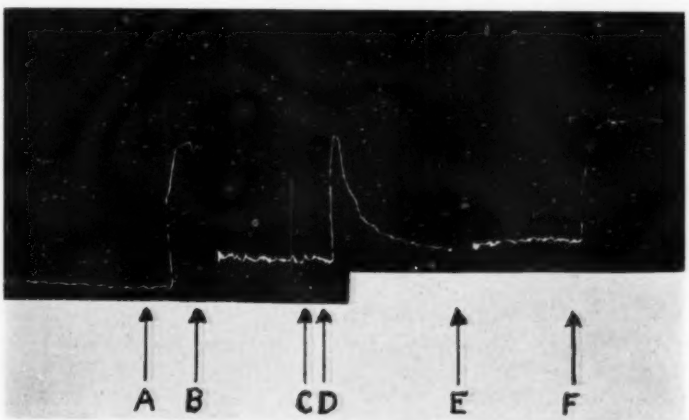

FIG. 1. ACTION OF ARGININE ON HISTAMINE

At A, C, and F 4 gamma histamine was added to the bath. At D 2 cc. arginine $\frac{1}{2}$ mol. was given at the height of the histamine contraction. At B and E Tyrode solution was changed.

followed up at once with 2 cc. $\frac{1}{2}$ molar solution of arginine. The muscle contraction starting on addition of histamine gave way to an immediate relaxation. After changing the bath the same strip responded again with a lasting contraction to 4 gamma histamine (fig. 1). In a different strip addition of 3 cc. arginine, $\frac{1}{2}$ mol. solution, to the bath completely prevented the effect of 5 gamma histamine, while 5 gamma acetylocholine produced a marked contraction. After change of the bath the same strip responded again to 5 gamma histamine (fig. 2).

The intestinal strip of a guinea pig sensitized with 0.5 cc. sheep serum intraabdominally 3 weeks prior to the Dale test reacted to 0.25 cc. sheep serum with a good contraction. A second piece of the strip was suspended and 5 cc. arginine $\frac{1}{2}$ molar solution was added to the bath. Two minutes later 0.25 cc. sheep serum were introduced; no contraction occurred. 5 gamma histamine also failed to induce a contraction. A typical reaction, however, resulted from 5 gamma acetylcholine. After washing out the strip no response again was

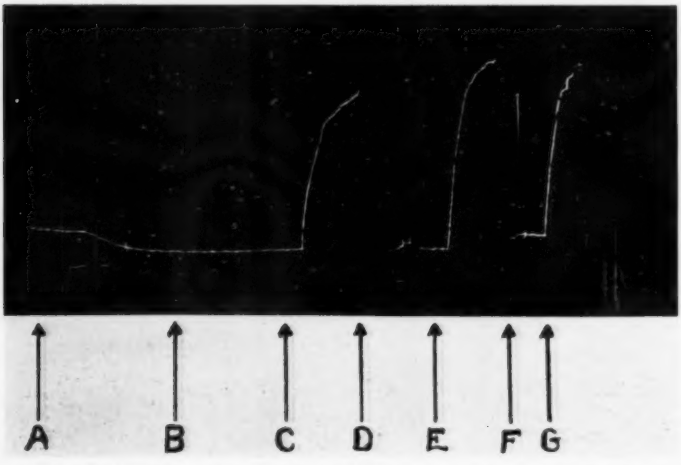

FIG. 2. ACTION OF ARGININE ON HISTAMINE AND ACETYLCHOLINE

At A 3 cc. arginine $\frac{1}{2}$ mol., at B and E 5 gamma histamine, at C and G 5 gamma acetylcholine were added to the bath. At D and F Tyrode solution was changed.

obtained to sheep serum, but 5 gamma histamine now brought about a contraction. The contraction due to 5 gamma acetylcholine after a second change of the bath was markedly stronger than the one following the addition of arginine (fig. 3).

Similar suppression of the histamine effect and the serum effect was seen by using histidine monohydrochloride (Merck) instead of arginine. 5 cc. histidine, $\frac{1}{2}$ molar solution, neutralized with KOH, inhibited the contraction which would have resulted from 20 gamma histamine (this intestinal strip was less sensitive and a larger dose of histamine

had to be used for the test). After changing the bath, this dose of histamine again elicited a contraction. The bath was changed again and 20 gamma histamine added once more; when the contraction

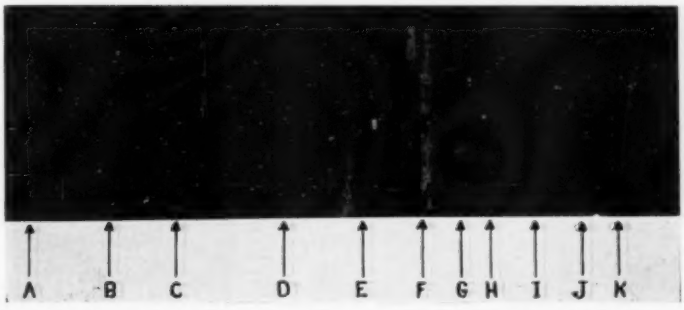

FIG. 3. ACTION OF ARGININE ON SHEEP SERUM, HISTAMINE, AND ACETYLCHOLINE

At A, D, and H 0.25 cc. sheep serum, at C 5 cc. arginine ½ mol., at E and I 5 gamma histamine, at F and K 5 gamma acetylcholine were added to the bath. At B a new piece of intestine was suspended. At G and J Tyrode solution was changed.

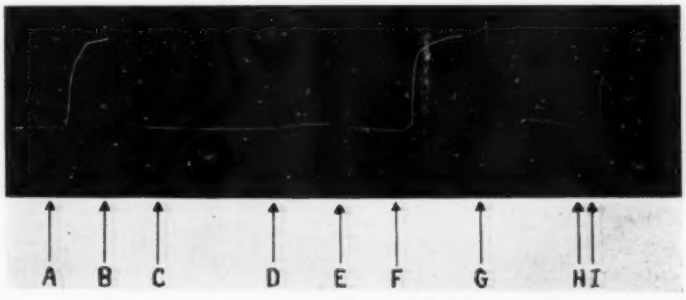

FIG. 4. ACTION OF HISTIDINE ON HISTAMINE

At A, D, F, and H 20 gamma histamine, at C and I 5 cc. histidine ½ mol. were given. At B and G Tyrode solution was changed. At I histidine was added after the histamine contraction had just started.

started, 5 cc. ½ molar solution of histidine was introduced and an immediate cessation of the contraction resulted (fig. 4). The effect of acetylcholine was not suppressed by histidine (fig. 5). In some experi-

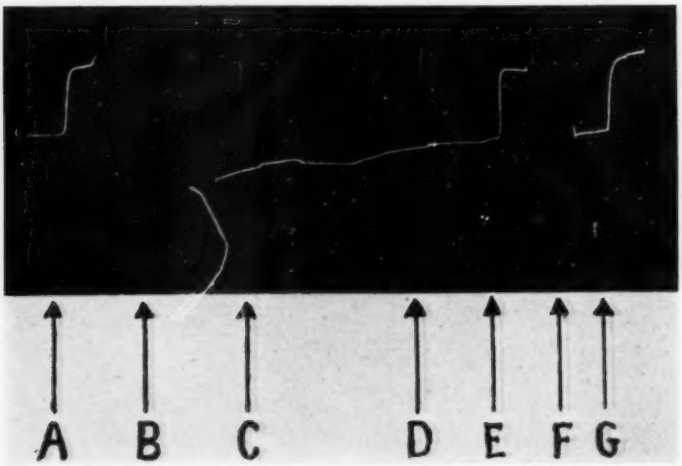

FIG. 5. ACTION OF HISTIDINE ON HISTAMINE AND ACETYLCHOLINE

At A and E 5 gamma acetylcholine, at D and G 5 gamma histamine, at C 5 cc. histidine ½ mol. were added to the bath. At B and F Tyrode solution was changed.

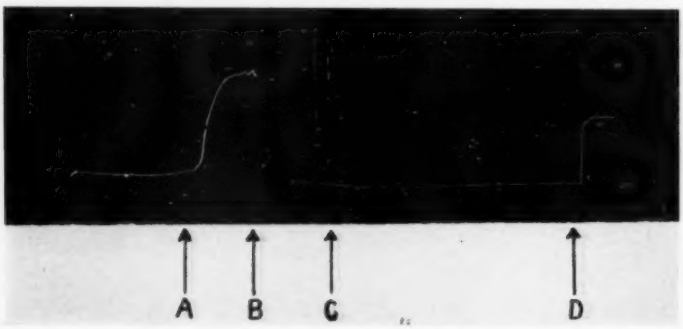

FIG. 6. ACTION OF HISTIDINE ON ACETYLCHOLINE

At A and D 30 gamma acetylcholine, at C 3 cc. histidine ½ mol. was given. At B Tyrode solution was changed.

ments, however, the contraction due to acetylcholine was considerably less in the bath containing histidine than in the pure Tyrode solution (fig. 6). Repeated controls showed slight variations in this respect.

While the experiment shown in fig. 8 seemed to indicate that histidine has a certain depressing effect on acetylcholine while arginine has not, there was no confirmation of such a difference in a subsequent experiment (fig. 9).

When histidine preceded the addition of sheep serum to the strip of a sensitized guinea pig, the antigen effect was entirely inhibited, as was the case in the arginine tests; the strip also failed to react to serum after the bath was changed, yet it responded again to histamine (fig. 7).

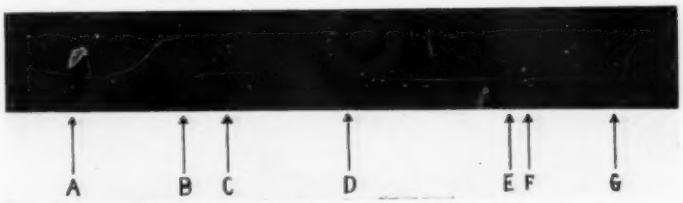

FIG. 7. ACTION OF HISTIDINE ON SHEEP SERUM

At A, D, and F 0.25 cc. sheep serum, at C 5 cc. histidine ½ mol., at G 10 gamma histamine were given. At B a new piece of intestine was suspended. At F bath was changed.

II. ACTION OF ARGININE ON HISTAMINE INTOXICATION OF THE GUINEA PIG

Our attempts to verify the experiments reported by Linneweh were hampered by technical difficulties. This author states that he killed 8 or 9 out of 10 guinea pigs of 300 gm. weight by intravenous injection of 50 gamma histamine or by intraabdominal injection of 100 to 200 gamma histamine. This would indicate a minimal lethal dose of approximately 0.16 mg. histamine per kg. intravenously. While a few authors could kill 90–100% of their guinea pigs with doses ranging from 0.3 to 0.4 mg. per kg. of histamine (Smith-Karady (6), Wilcox and Seegal (7)), the majority of workers seem to agree on 0.5 mg. per kg. as the minimal dose which reliably kills guinea pigs when injected in the blood stream (Dale and Laidlaw (8), Staub (9), Youngner and co-workers (10), Rosenthal and Brown (11)). Farmer and Fribourg (12) recently had only 11.9% deaths with 0.3 mg./kg., and 34.6% deaths with 0.35 mg./kg. histamine given intravenously. It is very

difficult to explain how Linneweh could have obtained 80 to 90% deaths with as little as 0.16 mg./kg. Our own numerous control

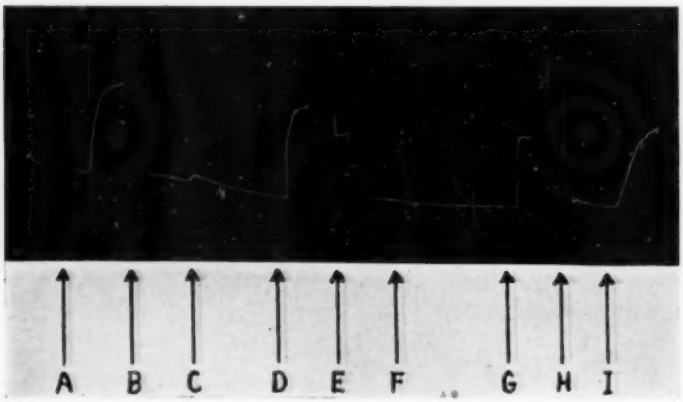

FIG. 8. ACTION OF ARGININE AND HISTIDINE ON ACETYLCHOLINE AND HISTAMINE

At A, D, and G 30 gamma acetylcholine, at C 3 cc. arginine ½ mol., at F 3 cc. histidine ½ mol., at I 30 gamma histamine were given. At B, E, and H Tyrode solution was changed.

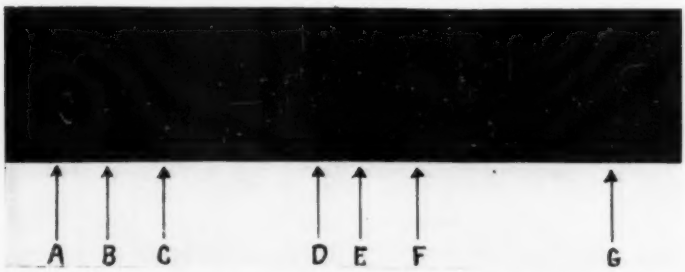

FIG. 9. ACTION OF ARGININE AND HISTIDINE ON ACETYLCHOLINE

At A, D, and G 30 gamma acetylcholine, at C 3 cc. arginine ½ mol., at F 3 cc. histidine ½ mol. were given. At B and E Tyrode solution was changed.

experiments shown in table I gave the following results: 53.8% deaths with 0.4 mg./kg., and 92.3% deaths with 0.5 mg./kg., given intracardially (Table I). We, therefore, considered 0.5 mg./kg. the smallest

TABLE I

Effect of Arginine on Histamine Intoxication in Guinea Pigs

a) Controls

NUMBER OF ANIMALS	DOSE OF HISTAMINE PER KG. INTRACARDIAC	DEAD	SURVIVED
	mg.		
13	0.4	7	6
13	0.5	12	1
8	0.6	7	1

b) Arginine

NUMBER OF ANIMALS	DOSE OF ARGININE	ROUTE OF INJECTION OF ARGININE	DOSE OF HISTAMINE	TIME OF HISTAMINE INJECTION	DEAD	SURVIVED
			mg./kg.			
3	1 gm. 40% sol.	i.a.	0.6	After 4 hours	3	0
4	1 gm. 40% sol.	i.a.	0.6	After 24 hours	3	1
3	1 gm. 40% sol.	i.a.	0.5	After 24 hours	3	0
8	1.5 gm. 40% sol.	i.a.	0.5	After 24 hours	4*	4
12	1 gm. 10% sol.	i.a.	0.5	After 4 hours	4†	8
6	1 gm. 10% sol.	i.a.	1.0	After 5 hours	2	4
3	0.1 gm. 40% sol.	heart	0.5	After 15 min.	2	1
3	0.2 gm. 40% sol.	heart	0.5	After 15 min.	2	1
4	0.25 gm. 40% sol.	heart	0.5	After 15 min.	3	1
10	0.4 gm. 40% sol.	heart	0.5	After 15–30 min.	1	9
1	0.8 gm. 40% sol.	heart	0.75	After 20 min.	0	1
3	0.8 gm. 40% sol.	heart	1.0	After 15–30 min.	1‡	2

* Two in delayed shock.
† 3 in delayed shock.
‡ After 27 min.

amount which would kill at least 90% of our guinea pigs when given in the blood stream.

As to the intraperitoneal route, it was found by Barlow and Hamburger (13) that 4 mg. per kg. were required to kill his animals while Rose and Brown (14) even had to give as much as 30 mg. per kg. (all values expressed as histamine base). Compared with only 0.33 to 0.66 mg. per kg. in Linneweh's guinea pigs this is again a striking difference!

A second difficulty arose from the scarcity of details in the German author's paper. It is not made clear what concentration of arginine was used in the intraabdominal injections. We employed first a 40% solution (arginine is readily soluble in water) and found that after 4 hours the abdomen still contained large amounts of clear fluid. After 24 hours complete resorption had occurred. The rate of absorption with a 10% solution was only slightly better. The large majority of the animals used in the experiments with 10% arginine presented large amounts of fluid 4 hours after the intraabdominal injection. This fluid was always clear in the histamine animals, but was sometimes bloody in the anaphylaxis experiments.

The results with the intraabdominal technique were, in keeping with the uncertain and variable factor of absorption, far from satisfactory. 1 gm. arginine in 40% solution gave no protection in a small series when followed 4 hours later by 1 MLD histamine. The same injection failed to give any protection in 7 animals when histamine was given 24 hours later; at this time, as mentioned, the whole amount apparently had been absorbed. We then tried to increase the dose of arginine, assuming that according to our much higher MLD of histamine more arginine might be needed for protection. The results were definitely better. 50% of the guinea pigs survived one MLD of histamine 24 hours after an intraabdominal injection of 1.5 gm. of arginine in 40% solution. It seemed, however, that this dose was approaching the limits of tolerance, for the injection of even 1 gm. arginine made the guinea pigs distinctly sick. They had usually recovered fairly well after 4 hours, completely after 24 hours. 1.5 gm. given intraabdominally caused death in 7 out of 10 animals apparently due to toxic effect of the substance. In another series all 10 animals died following the i.a. injection of 2 gm. arginine.

When we changed to a 10% solution the results were more favorable. Out of 12 guinea pigs injected with 1 gm. arginine, 8 survived one MLD

of histamine given 4 hours later; of the 4 animals who died following the histamine injection, 3 died in distinctly delayed shock. Six of the surviving animals were reinjected with 2 MLD about 20 to 30 minutes later, and four of them again survived. One of the animals who had survived 2 MLD, died promptly following a single lethal dose of histamine 3 days later.

We then decided to abandon the intraperitoneal route with its complicating factor of uncertain absorption, and injected the arginine solution intravenously, or, in most of the cases, intracardially. (While our work was in progress, we found that Staub in France, followed by Wilcox and Seegal in this country, also had chosen the injection in the bloodstream in their studies on the inhibition of anaphylaxis with a different agent.) Arginine in 40% solution was very slowly injected 15 minutes prior to the histamine injection. We found that two cardiac punctures in short succession involved a considerable loss of animals from hemorrhage. We discarded all animals when the autopsy revealed hemorrhage of the heart as a possible factor in the death of the guinea pig. All guinea pigs which died in the course of any of our experiments were subjected to dissection of the chest and the abdominal cavity.

As Table I shows, doses of arginine ranging from 0.1 to 0.25 gm. failed to prevent death in 7 out of 10 animals. Stepping up the dose to 0.4 gm. gave the remarkable result that 9 out of 10 guinea pigs survived the subsequent administration of one MLD of histamine. All these animals had breathing difficulties, became weak and listless for a certain period of time, some of them also had cough and convulsions, but they recovered completely in a short time. While the injection of arginine in doses up to 0.4 gm. was well tolerated if given slowly enough, increase in dosage resulted in serious reactions in a number of animals; in some instances violent trembling developed, followed by general weakness. When 0.6 or 0.8 gm. arginine was given, about 50% of the guinea pigs died from the arginine injection. The autopsy in these cases revealed very small, hemorrhagic lungs and, in some cases, dilatation of the heart. The number of guinea pigs in which we could use higher doses was therefore small. In 4 animals which received 0.8 gm. arginine intracardially, the resulting protection against histamine was very impressive. One of these animals survived $1\frac{1}{2}$ MLD and two

survived 2 MLD. One of the guinea pigs which had recovered from 2 MLD of histamine was sacrificed after 25 minutes. The autopsy showed very slight distention of the lungs, and one lung lobe was slightly hemorrhagic. Some weeks later the guinea pig which had survived the administration of 1½ MLD of histamine after arginine injection was reinjected with 1 MLD of histamine and died promptly. It is worth while mentioning that the 1 animal which had received 0.8 gm. arginine and had died after 2 MLD of histamine, showed only general weakness, without respiratory symptoms or convulsions or cyanosis, after histamine was given. The lungs were small and not distended; they were hemorrhagic, as were the intestines and the whole picture reminded one of the findings in those animals who had succumbed to the simple arginine injection in higher doses. The animal had been seriously ill after the arginine had been given, but seemed to have completely recovered at the time of the histamine injection.

III. ACTION OF ARGININE ON ANAPHYLACTIC SHOCK OF GUINEA PIGS

Wide discrepancies in the sensitizing and shocking doses required to obtain death in anaphylactic shock in guinea pigs have been observed by many workers. Richet (15) in France discussing this problem states that the guinea pigs in Europe, in the United States, and in Brazil seem to react differently. We were unable to adopt Linneweh's figures of 0.1 cc. serum as a sensitizing dose and 0.2 cc. as shocking dose, as we obtained only 50% death in anaphylactic shock with this technique in 18 animals. After many trials we finally succeeded in obtaining an average 80% death in anaphylactic shock with the following technique: 0.5 cc. freshly prepared sheep serum were injected intraabdominally; 23 to 27 days later the guinea pig received 0.25 cc. sheep serum intracardially as shocking dose. 0.25 cc. seemed to be the minimal dose sufficient to produce death in the sensitized guinea pig; two out of three animals survived when shock was attempted with 0.2 cc. serum.

The results of arginine injection preceding the shocking dose were very different from those in the histamine series. Not only did intraabdominal administration fail to provide any protection (8 out of 11 animals died in anaphylactic shock 4 hours after having received 1 gm. arginine in 10% solution), but the injection in the blood stream likewise

TABLE II

Effect of Arginine on Anaphylactic Shock in Guinea Pigs

	NO. OF ANIMALS	MATERIAL	DOSE	ROUTE	DOSE	ROUTE	TIME	DEATH IN ANAPHYLACTIC SHOCK	SURVIVED
		of sensitization			of reinjection				
			cc.		*cc.*		*days*		
Arginine 1 gm. i.a. 24 h. prior to reinjection (40% sol.)	10	Sheep serum	0.5	Intra - abdom.	0.25	Heart	26	9	1
Controls	5	Sheep serum	0.5	Intra - abdom.	0.25	Heart	23	4	1
Arginine 1 gm. i.a. 4 h. prior to reinjection (10% sol.)	11	Sheep serum	0.5	Intra - abdom.	0.25	Heart or i.v.	23–27	8	3
Controls	8	Sheep serum	0.5	Intra - abdom.	0.25	Heart	26	7	1
Arginine 0.4 gm. intracard. 15–30 minutes prior to reinjection (40% sol.)	11	Sheep serum	0.5	Intra - abdom.	0.25	Heart	25–28	8	3
Controls	8	Sheep serum	0.5	Intra - abdom.	0.25	Heart	23	6	2
Arginine 0.6 gm. intracard. 15–30 minutes prior to reinjection (40% sol).	6	Sheep serum	0.5	Intra - abdom.	0.25	Heart	28–30	5	1

had no noticeable effect. Eight out of 11 guinea pigs also died when the intracardial injection of 0.4 gm. arginine (in 40% solution) was followed 15 to 30 minutes later by the shocking dose, and 5 out of 6 animals died in spite of the intracardial injection of as much as 0.6 gm. arginine preceding the shocking dose (Table II). The guinea pigs developed the typical shock syndrome, and autopsies revealed huge distended lungs in every instance. After the injection of 0.8 gm. arginine intracardially in 1 animal the shocking dose again produced the common picture presenting cough, violent scratching, asthma and weakness. Death, however, did not occur until 20 minutes later, and autopsy showed no distention of the lungs which had hemorrhagic dots on the surface and were similar in aspect to those found in animals which died after arginine injection alone.

DISCUSSION

There can be no doubt that arginine and histidine are able to prevent the intestinal strip of the guinea pig from reacting with a contraction to histamine and antigen.

Ackermann and Wasmuth considered the arginine inhibition a reaction strictly specific for histamine and reported that the response to choline was not influenced by arginine. Rothlin (16), however, found that arginine also inhibited in some degree the action of pitocin, and Linneweh observed an inhibiting or depressing effect of arginine on sodium acetate, sodium citrate, and peptone. As to histidine, the studies of Mackay (17) and Halpern (18) demonstrated that it has an inhibiting effect not only on histamine but also, though to a lesser degree, on substances such as peptone, acetylcholine, eserine, and barium chlorate. In our own observations the action of acetylcholine was not suppressed by such doses of arginine or histidine which prevented histamine contraction in the intestinal strip. However, while in some tests there was no important difference in the acetylcholine curve no matter whether arginine or histidine was employed or not, in other experiments the contraction was decidedly weaker when one of these substances had been added to the bath, compared with the contraction in pure Tyrode solution. Thus we are lead to the conclusion that absolute specificity for arginine or histidine to prevent histamine contraction in smooth muscles cannot be claimed.

The question might arise whether there is any specific effect at all in the inhibitory action of these amino acids, or whether they exert simply a certain depressing effect on smooth muscle cells. Mackay's statement that addition of histidine to the bath caused slight relaxation of tone and inhibition of spontaneous movements of the gut, would fit in such an assumption; we have also seen relaxation of the tone of the muscle on addition of arginine or histidine to the bath in some instances. The difference in the inhibitory effect towards different substances could then be explained on a purely quantitative basis, related to the strength of the stimulation by those different agents. We intend to undertake a study of this question.

As to the effect on the ileum of the sensitized guinea pig, we confirm Ackermann and Wasmuth's observation that desensitization occurs by adding serum to the bath although contraction of the strip is prevented by arginine or histidine; for the same strip fails to react to serum after the bath has been changed, whereas a prompt response to histamine then can be obtained.

Our results with the administration of arginine in the whole animal did not correspond to those of Linneweh.

Difference in the results of the attempts to prevent histamine death can be explained by method changes made necessary by higher tolerance to histamine in our guinea pigs. Intraabdominal preparation of the animals with 1 gm. arginine in 10% solution protected only $66\frac{2}{3}\%$ of them against 1 MLD of histamine (some of them even against 2 MLD). But injection of 0.4 gm. arginine in 40% solution in the blood stream saved 90% of the animals receiving 1 MLD, and 0.8 gm. arginine intracardially protected against 2 MLD in 3 out of 4 animals. Contrary to Linneweh, however, all the animals who survived had respiratory difficulties and other common signs of histamine intoxication. Autopsies of such animals revealed only slight distention of the lungs compared with those who died in histamine shock.

Our experiments with prevention of anaphylactic shock by preparing the guinea pigs with arginine were entirely negative. Here again we had to use higher doses in sensitizing and shocking the animals than Linneweh. Intraabdominal administration as well as intracardial doses of arginine were unable to save the guinea pigs from death in typical anaphylactic shock, confirmed by huge distention of the lungs in autopsies.

We tested a 2% solution of arginine intradermally in men, and failed to see any effect on the outcome of intradermal tests with histamine or with pollen extract in sensitive patients, regardless whether given together with these substances, or if injected in the fully developed skin wheal.

Staub, of the Pasteur Institute, who had excellent results with two ethylenediamines (929 F and 1571 F) in preventing histamine reactions and anaphylactic reactions, likewise failed to obtain any effect of her material on intradermal skin reactions produced by histamine.

Staub's extensive studies which unfortunately cannot be reviewed here due to lack of space, offer some interesting aspects in comparison with the work done with arginine and histidine. Rosenthal and Brown confirmed her observation that 929 F inhibited histamine contraction and antigen contraction in the intestinal strip, and prevented the death of guinea pigs from histamine shock and from anaphylactic shock. Wilcox and Seegal used Staub's preparation 1571 F and could protect guinea pigs against as many as 6 MLD of histamine and against up to 4 MLD of antigen; in studies of the isolated heart they observed that the characteristic slowing of the coronary flow following addition of histamine or antigen was prevented by 1571 F, or that the flow was even increased.

If we analyze the studies done by Ackermann and Wasmuth with arginine, and those undertaken with the two French preparations, we note that larger doses were used in preventing antigen effects than in preventing histamine effects on the isolated organs of the guinea pig. Wilcox and Seegal stress this point in their article while the other authors apparently paid no attention to it. As to the experiments in the intact guinea pig, the studies of Staub and those of Rosenthal and Brown do not permit a definite conclusion because the small numbers of animals used as controls renders the estimation of the minimal lethal dose of antigen in their animals unreliable. (We have seen repeatedly prompt anaphylactic death from a certain shocking dose in 3 guinea pigs, but survival from the same dose in the following three animals). Rosenthal and Brown, moreover, did not attempt to determine the maximum of protection obtainable with 929 F against histamine. But the experiments of Wilcox and Seegal seem to indicate that a larger protective dose was also needed for inhibiting the anaphylactic death than for inhibiting histamine death.

On the basis of such a difference in the dosage necessary for protection against histamine and against anaphylaxis we could explain the striking contrast in our results and those of Linneweh. The German author, who did not consider at all the quantitative factor, probably gave more arginine than needed to his guinea pigs which had an extraordinarily low minimal lethal dose for histamine, while the same dose of arginine was still adequate for protecting against anaphylactic death. Our guinea pigs, requiring much more histamine and antigen for lethal shock, could be protected against histamine with a dose of arginine which lay just below the limit probably of tolerance. A still higher dose of arginine, however, which would have accomplished protection against anaphylactic shock could not be given because of its toxicity.

The question, of course, arises how the different agents act in preventing the effects of histamine and antigen. Several suggestions have been made.

Staub concluded from her numerous experiments that 929 F and 1571 F are true antihistaminic drugs. Their action is not simply spasmolytic. The author believes that there is a particular property of these substances, hitherto unexplained, due to which only a small portion of histamine reaches the lungs of the protected animals. She emphasizes that the role of histamine in the anaphylactic shock is a complex one but she feels that the protective action of 929 F in anaphylactic shock adds a new argument in favor of the role played by histamine in this phenomenon. Rosenthal and Brown stated that 929 F does not neutralize histamine or antigen directly, but it antagonizes the action of histamine; incubation of 929 F with histamine for 2 hours failed to inhibit the histamine effect on the intestinal strip. This observation is not entirely in agreement with Staub who obtained a reaction much weaker than the common histamine reaction when she added a mixture of 929 F and histamine to the bath, though even after several hours the reaction to this mixture did not disappear, indicating that histamine had not undergone destruction. Rosenthal and Brown felt that primary tissue damage and substances other than histamine probably account for the prolonged malaise and prostration in the anaphylactic animals treated with 929 F, and for the death that sometimes terminates protracted anaphylactic shock, whereas the true signs of histamine liberation such as scratching, respiratory embarrass-

ments, convulsions and early death were suppressed. For they observed that the guinea pigs protected against histamine suffered no obvious respiratory difficulties, but experienced a moderate amount of malaise. After 10 to 15 minutes there was complete recovery. In the guinea pigs surviving reinjection of antigen after 929 F was given, respiratory difficulty, scratching, or convulsions "rarely" developed. These animals did show signs of malaise and prostration. This condition lasted for one to several hours. It seems doubtful how far it is possible to draw definite conclusions from the behavior of the animals. The reports of Staub and of Wilcox and Seegal concerning the symptoms of their animals are remarkably conflicting. Staub saw no shock symptoms at all in the guinea pigs protected by 1571 F against histamine, but shock symptoms did occur in those protected by 929 F against histamine and by the majority of those protected by 929 F against antigen. No details are given by this author as to the kind of shock symptoms she observed. Wilcox and Seegal, however, found shock symptoms in almost all guinea pigs protected by 1571 F, as well in those treated with histamine as in those treated with antigen. Respiratory difficulties were present, but they were less outstanding than prostration and cyanosis. Wilcox and Seegal conclude from their experiments that 1571 F acts primarily by preventing contraction of smooth muscles induced by histamine, but that other factors, also playing a part in anaphylactic shock, are not influenced.

The explanation offered by Ackermann and Wasmuth for the action of arginine and histidine is of a chemical nature. These authors assume that the effect of histamine is dependent on its imidazol nucleus whereas its imino group has to be available for its biological attachment. They suggest that the inhibiting action of arginine, histidine, and other substances on histamine is a kind of mass action of the imino group of these amino acids which prevents the fixation of the imino group of histamine. Contrary to what was seen in the studies with 929 F is the observation, which we are able to confirm, that a mixture of arginine and histamine fails to elicit the contraction of the intestinal strip which would have resulted from histamine alone. From the fact that arginine prevents the contraction of the sensitized intestinal strip which otherwise occurs on addition of the antigen, but does not prevent desensitization of the strip, the writers conclude that the antigen-

antibody reaction takes its course unimpeded by arginine, but that the amount of histamine liberated by the antigen-antibody reaction is prevented from having its effect on the muscle strip. In other words, only that part of the effects of an antigen-antibody reaction which is due to histamine is affected by arginine or histidine. (Rosenthal and Brown observed the same phenomenon in their studies; inhibition of contraction, but not of desensitization of the intestinal strip by 929 F.) As to the behavior of the animals protected by arginine, it is stated by Linneweh that the guinea pigs protected against histamine had no respiratory difficulties, but some shock symptoms, while the guinea pigs protected against antigen had no shock symptoms at all (the author untied the animals "some minutes" after having given the shocking dose, and might, therefore, have overlooked symptoms). As mentioned above, all our guinea pigs protected against histamine had shock symptoms including respiratory difficulties.

It is evident that all these explanations are only tentative and do not possess more than hypothetical value. The mechanism of the protective action of the amino acids arginine and histamine on the one side, and of 959 F and 1571 F on the other side, is apparently different in the two cases; the different results obtained with a mixture of arginine and histamine, and with a mixture of 929 F and histamine in the Dale test are particularly suggestive.

All the workers whose studies have been discussed here, apparently agree that the protection in the anaphylactic experiments is directed against histamine liberated in the course of the antigen-antibody reaction. While it is true that those studies, like others before, reveal a remarkable parallelism between histamine experiments and the anaphylaxis experiments, they do not furnish conclusive evidence that the anaphylactic symptoms are due to histamine. Ackermann and Wasmuth felt that histamine must definitely take part in anaphylactic shock because the antigen contraction can be prevented or stopped by arginine in the same specific way as the histamine contraction; this assumption proved to be erroneous when it became apparent that arginine is not strictly specific for histamine. The need for higher doses of the protecting agent in preventing antigen effects compared with those preventing histamine effects could be explained if we assume that histamine liberated by the antigen-antibody reaction is in more

intimate association with the tissue and therefore provides a stronger stimulus for the muscle cell than histamine added to the bath or injected in the animal.

We wish to emphasize, however, that the question whether histamine itself is liberated or something similar to it in the anaphylactic reactions, is far from settled. Lewis used the term H-substance, and this term should still be preferred. As long as the evidence for the presence of histamine rests only on biological methods instead of on chemical demonstration, a final decision can hardly be made.

We may call attention, in this connection, to the work of Tsuji (19), and to that of Kallos and Pagel (20). These authors found that the lungs of guinea pigs subjected to anaphylactic shock showed characteristic differences compared with the lungs of guinea pigs treated with histamine. Kallos and Kallos-Deffner (21) conclude from these histological studies that substances like histamine cannot play more than a secondary role in the genesis of bronchial asthma. Studies to verify these reports are under way.

It would be premature, to say the least, to expect any therapeutic value from the substances discussed here in preventing allergic or anaphylactic reactions. 929 F and 1571 F are certainly too toxic for such applications. The results with arginine do not justify high expectations if we keep in mind the relatively high doses that are required and the short duration of its effect. It might be that feeding experiments could give a better basis for considering such a possibility.

SUMMARY

1. Arginine monohydrochloride and histidine monohydrochloride are capable of preventing or stopping the effect of histamine or of an antigen on the intestinal strip of guinea pigs. The ileum of a sensitized guinea pig is desensitized by adding the specific antigen even if contraction of the strip is prevented by arginine or histidine. The action of acetylcholine on the intestinal strip is not suppressed by these amino acids but is sometimes weakened.

2. Death from histamine injection can be prevented in guinea pigs by a preceding administration of arginine monohydrochloride. Intracardiac injection is more effective than intraabdominal injection. All protected animals had respiratory difficulties beside other symptoms of histamine intoxication.

3. Arginine gave no protection against death in anaphylactic shock if doses similar to those used in the histamine experiments were given. In higher doses arginine was highly toxic.

4. Arginine in 2% solution had no effect on intradermal skin reactions from histamine or pollen extract in patients.

5. From our studies and from those of authors who prevented effects of histamine and of anaphylaxis by using the French preparations 929 F and 1571 F, it seems that higher doses of the protecting substances are needed for preventing anaphylactic effects than for preventing histamine effects.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Spontaneous and Experimental Leukaemia in Animals. By JULIUS ENGELBRETH-HOLM. Translated from Danish into English by C. L. Heel. 245 pp. Illus. 15 shillings. Oliver and Boyd, Edinburgh and London, 1942.

The accumulation of known information about leukemia in animals as a sort of summary up to the outbreak of the war by Dr. Julius Engelbreth Holm should be of considerable interest to anyone concerned with the problems of human leukemia. One might assume that studies of leukemia in animals might have progressed more rapidly than the studies of the human disease syndromes, but reviews of the history of the study of the forms of animal leukemia and summary of the experimental phases leaves one with the impression that such is not the case.

It is of interest that in mammalian and bird leukemia, there is an absolute preponderance of lymphogenous leukemia and lymphosarcoma. The seasonal occurrence and variation in lymphogenous leukemia in fowls has no obvious counterpart in human or mammalian leukemia.

Transmission experiments are described in some detail and the difficulties of distinguishing between pure leukemia and lymphosarcoma and the difficulties of distinguishing between leukemic and non-leukemic cases are emphasized. Inbred strains of animals are of importance in transmission experiments. Animal studies would tend to confirm the impression that leukemic cells are not normal younger cells but that the proliferating cell in lymphogenous leukemia for example is a pathological malignant lymphocyte with limited power of maturation and the proliferating cells in myelogenous leukemia are pathologic neoplastic myelocytes. In general, the features of animal leukemia are presumably analagous to those of other forms of tumor. The importance of carcinogenic hydrocarbons, x-rays, and probably estrogenic substances in the development of leukemia are noted.

An extensive bibliography is appended.

R. N. T.

The Interaction of Drugs and Cell Catalysts. By FREDERICK BERNHEIM. 85 pp. 8½ x 11 inches, paper covers, mimeoprinted. $2.25. The Burgess Publishing Co., Minneapolis, 1942.

Brief reviews of various aspects of the subject with bibliographies.

Quotations from the Preface will indicate the intended scope of this booklet.

"For most of the drugs the correlation between enzyme and pharmacological action is incomplete.... It is, perhaps, the main purpose of this review to emphasize the difficulties in order that further work may prove or disprove the value of this particular method of approach.

"For each drug only the pharmacological effects are described that are pertinent to the particular enzyme action under consideration. . . . The drugs that have been included are those that have not before been fully discussed from the point of view of correlating their *in vivo* and *in vitro* effects."

Under Part I are discussed effects of eserine, morphine, strychnine, curare, and methylene blue upon the activity of the enzyme, cholinesterase; and of cyanide, selenium, arsenic, copper, sulfanilamide, and salicylate upon certain other enzymes. Part II deals with six different "drugs that are acted on by certain enzymes."

L. H.

How to Live in the Tropics. By VIRGINIA LLOYD HUNT. 178 pp. $2.00. Harcourt, Brace and Company, New York, 1942.

This handbook offers suggestions for meeting the special problems resulting from climate and from primitive conditions in many parts of the tropics. It is intended primarily for people who are going to make their residence in the tropics, as well as for tourists. Written in a popular vein, it is very readable. The author's comments on trips to the field may be considered applicable to the book as a whole, when she states that her "suggestions are not designed for the scientist or explorer, who will have all his information before he ever leaves home. These are for the amateur."

The amateur is given helpful advice on preparations for the trip, how to cope with climate and environment, what to eat and drink, the importance of hobbies, and the particular worries of women and children. Special emphasis is given to sections on disease and nursing.

It is unfortunate that some of the recommendations refer to methods of protection and comfort used in the past but no longer in general practice, such as the use of red cloth to prevent penetration of actinic rays. The individual adopting the suggestions on what to take along would undoubtedly be well-equipped, but the material recommended would probably exceed the needs in many areas.

The author is to be especially commended for stressing the importance of obtaining specific data on the particular spot in which residence is to be established, or the places to be visited, and the need for consultation with a physician regarding the diseases in particular areas. Notable omissions from the table of communicable diseases found in the tropics are epidemic meningitis, leishmaniasis, poliomyelitis, schistosomiasis and trypanosomiasis.

The opinion of many outstanding authorities has been summarized, and there is an appendage of a list of useful books.

C. H. Y.

War Medicine. A Symposium. Edited by WINFIELD SCOTT PUGH [and others]. 565 pp. Illus. $7.50. Philosophical Library, New York, 1942.

Much of the material contained in this symposium volume has already been published in various medical and surgical journals. In as much as many civilian

as well as military physicians in this country have already been or will be confronted with the duty of providing the first medical treatment to large numbers of casualties produced by modern warfare, a concise volume such as this is most essential. The unfamiliar nature, to the average practitioner or house physician, of many of these injuries and the importance of early and efficient application of proper measures for their treatment emphasize the value of a reliable source of practical information which this volume presents in an orderly, indexed, well written, brief, yet concise manner by authors who are recognized authorities. The volume presents a comprehensive review of injuries of the various body parts and systems, such as the brain and spinal cord, ocular and auditory systems, abdominothoracic injuries and fractures. The sections on shock, anesthesia, blood and blood substitutes are amply covered and well illustrated. Included are splendid papers on aviation medicine, cardiology, nutrition and psychiatry. The proper application of early measures of treatment, as outlined in the book, may eliminate, at least in some instances, the need for much later specialized treatment.

K. P.

Indigestion: Its Diagnosis and Management, with Special Reference to Diet. By MARTIN E. REHFUSS. 556 pp. Illus. $7.00. W. B. Saunders Company, Philadelphia and London, 1943.

This monograph will be of great interest to the medical profession in general and should prove to be an invaluable aid in dealing with the problem of "indigestion". The symptom complex under discussion is universal and, unless carefully studied and expertly analyzed, will in many instances result in mistaken diagnoses leading to irreparable harm, since, as we know, such lesions as ulcer and carcinoma often masquerade in the form of indefinite discomfort, pain, and a host of other symptoms. A busy practitioner may ignore such perils until "too late" unless he is fully alive to the implications of *any* reported symptoms, even though not severe or outstanding.

The author presents the various chapters in a thorough and clarifying manner, starting with "indigestion" and carrying on through history-taking, physical diagnosis, gastric and duodenal analysis, and X-ray. He also explains in detail the relationship of indigestion to infection, gastric functional disturbances, and other conditions, thus providing a needed guide and help to both medical student and internist. The chapter on "Indigestion of Old Age" is particularly useful and a most welcome presentation, as is his splendid exposition regarding reflex indigestion. Again, the author is to be highly commended on his full and authoritative chapters on diet, and therapy in general in dyspeptic states.

Of especial interest and importance are the chapters contributed by Dr. Philip Hawk on vitamins and water.

The reviewer can confidently recommend this excellent book to student and practitioner alike.

E. H. G.

Introduction to Materia Medica and Pharmacology. By HUGH ALISTER MCGUIGAN and ELSIE E. KRUG. 3rd ed. 779 pp. Illus. $3.50. The C. V. Mosby Company, St. Louis, 1942.

The book is for nurses and seems admirably adapted to its purpose.

There are introductory chapters on Pharmacy, an Arithmetic Review, Weights and Measures and The Administration of Medicines. The remainder of the work is Pharmacology, well arranged and with brief, direct, and succinct statements and descriptions. It is up to date. Among other useful features, there is an appendix with several pages of synonymous terms, a good glossary of 15 pages, and an excellent index.

The Illustrations are satisfactory and the print excellent.

T. P. S.

Endoscopic Prostatic Surgery. By ROGER W. BARNES. 232 pp. Illus. $6.00. The C. V. Mosby Company, St. Louis, 1943.

This small volume on the highly specialized and controversial subject of transurethral resection should be welcomed by all urologists. Dr. Barnes describes briefly the history of the development of this procedure and emphasizes the fact that the technical developments which have been made possible are dependent on the advances which the physicists and electrical engineers have accomplished.

There is a short but adequate chapter on the surgical anatomy of the prostate gland with special reference to the blood supply, which is, of course, of paramount importance in transurethral resection. The chapter on the pathology of prostatism is quite short, but the different types of enlargement which one may encounter clinically are well described. The examination of the patient and the indications for operation are carefully and conservatively discussed, and the author very properly emphasizes the fact that under no consideration should transurethral resection be considered a "minor operation." Indeed it should be regarded as one of the most difficult procedures that the urologist may be called upon to perform. The pre-operative investigation and care of the patient have done much to reduce the appalling mortality which occurred in the early days of prostatic surgery, but the author makes little or no mention of the pre-operative use of the sulfonamides which have been demonstrated to be of the utmost importance in the prevention of postoperative morbidity and infection.

A comprehensive chapter on the technique of transurethral prostatectomy follows which should be extremely helpful to all doing transurethral work. The author's methods are simple, practical, and concisely explained. The illustrations are entirely adequate, although somewhat diagrammatic. Rather in contrast to the conservatism of the author is the chapter on punch prostatectomy by H. C. Bumpus, Jr. This method is extolled beyond all other methods of prostatic surgery. The controversial subject of multiple operations is discussed and many urologists, I am sure, would question the statement that "The fact that multiple stage operations are possible with transurethral resections and punch prostatec-

tomies is one of the reasons why these can be undertaken on patients whose physical condition would never permit open prostatectomy, either suprapubic or perineal." In many clinics it is the impression that either suprapubic or perineal prostatectomy can be carried out with no more shock or danger than an extensive transurethral procedure, and the statement that two or even three operations might be easier on the patient than a single one is certainly open to question.

Dr. Barnes concludes his book with an adequate discussion of the immediate complications and a chapter on postoperative care, the importance of which he particularly stresses. A final chapter on the results and sequelae presents the whole subject in a very conservative manner.

J. A. C. C.

Aviation Medicine. By LOUIS HOPEWELL BAUER. Edited by HENRY A. CHRISTIAN. 50 pp. Illus. $1.50. Oxford University Press, New York [etc.] 1943. [Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work.]

This excerpt from the Oxford Loose-Leaf Medicine is a brief, systematic review of problems encountered in flight as well as in selection and care of personnel. The material is presented in simple terms and without great elaboration.

J. L., Jr.

Manual of Clinical Therapeutics. By WINDSOR C. CUTTING. 609 pp. $4.00. W. B. Saunders Company, Philadelphia and London, 1943.

The treatment of almost every variety of disease is described with great conciseness. A few references to the literature are appended to each section. The brevity is admirable but leads to occasional categorical statements which would be difficult to defend in their broadest interpretation. In general, this book should be valuable as a therapeutic primer in the more common diseases and as a ready source of information and references on the treatment of the less common diseases.

J. L., Jr.

Principles and Techniques of Nursing Procedures. By SISTER MARY AGNITA CLAIRE DAY. 574 pp. Illus. $3.50. The C. V. Mosby Company, St. Louis, 1943.

This book has been compiled by members of the nursing staff of the St. Mary's Group of Hospitals of St. Louis University. It is an outgrowth of the procedure manual used in those institutions. It is the author's aim to present techniques in a simple manner and to emphasize underlying principles in order that these techniques may be adapted to any situation.

The subject matter is divided into five parts:—Part I is concerned with Nursing Activities Associated with the Environment of the Patient. Part II discusses the Admission Procedure and Simple Diagnostic and Therapeutic Measures. Part III deals with Nursing Techniques Involved in Diagnostic Tests and in Prophylactic

and Remedial Measures. Part IV presents Special Orthopedic Devices and Treatments and Part V is titled The Psychiatric Patient in the General Hospital.

Each technique is presented in a uniform manner and includes a discussion of purposes for which it is done, a brief reference to basic principles in the form of general instructions, a list of equipment necessary, an outlined procedure and a list of points to be considered in recording observations. There are 94 illustrations, the majority of which are photographs, useful for comparative purposes. The bibliography which is placed at the end of each section includes authoritative sources. However, the scientific bases of principles on which the techniques are constructed are not clearly indicated.

The psychologic needs of the patient are discussed very well but very briefly in Part II while Part V is concerned with the many techniques used in the care of the acutely ill psychiatric patient and presupposes special preparation of the nurse as well as segregation of patients in a separate division of the hospital. It is unfortunate that discussion of the psychologic aspects of the nursing care of the patient in the general hospital is not amplified.

There is little discussion of the responsibilities of the nurse for disease prevention and for health teaching.

Diagnostic tests are described in detail in Part III. Because the details of these tests vary so frequently, the value of this information outside the institution in which the described tests are used is questionable.

This volume is impregnated with the teachings of the Catholic Church. At every opportunity application of the Catholic philosophy is made to nursing situations. It is especially useful as a source of information for Catholic nurses but its complete discussion of the religious needs of the Catholic patient should prove helpful to all nurses striving to give more understanding care regardless of their own religious affiliations.

It has a very definite place among reference books for student and graduate nurses, especially when they are concerned with comparison of nursing techniques.

E. H.

Textbook of Anatomy and Physiology for Nurses. By CARL C. FRANCIS, G. CLINTON KNOWLTON and W. W. TUTTLE. 586 pp. Illus. $3.50. The C. V. Mosby Company, St. Louis, 1943.

The first few chapters of this book give a picture of the body as a whole. Through this introductory material the student is well oriented for the subsequent detailed anatomy and physiology. The main body of the book is divided into five well integrated units, each of which is subdivided into logical chapter groupings. This organization assists the student in visualizing the interdependence and interrelationship of the organ systems.

Contained in the text are numerous colored plates and drawings and several illustrations not ordinarily found in nurses' textbooks. Often different views of the same specimen are given, thus aiding the student in visualizing the three dimen-

sional aspect. Muscular movement is well illustrated in unusual diagrammatic drawings. All of this illustrative material serves to make the book interesting and readable.

In view of the fact that student nurses are given a limited time in which to pursue the study of anatomy and physiology, I feel that this book, concise, yet complete, is particularly desirable.

W. S.

Discovering Ourselves. A View of the Human Mind and How It Works. By EDWARD A. STRECKER and KENNETH E. APPEL. 2nd ed. 434 pp. Illus. $3.00. The Macmillan Company, New York, 1943.

"This book," the authors say, "is meant to be entirely practical. It is not written for psychologists or psychiatrists. It does not aim to discuss theoretical questions. Abstract discussions are introduced only in so far as they throw light on the practical problems of nervousness and teach how they may be dealt with and solved." Many popular presentations of mental hygiene which have started out with a similar program have managed to confuse rather than enlighten the reader. This book, the first edition of which appeared in 1931, has done magnificently what it had set out to do. It is written clearly, simply, with an eye on everyday living, with emphasis on the common problems and puzzlements which everybody is apt to—and does—encounter. The examples and illustrations are drawn from universal experience.

The first of two parts describes and explains "the conceptions of modern psychology." Controversial matters are wisely omitted. Three chapters on "the nature of emotion, anger, and fear" by John W. Appel are meaty, lucid and readable. The second part deals with "mental mechanisms or typical ways in which the human personality meets conflicting urges and difficulties in every day life." Many misused and misinterpreted concepts are clarified in a semantically irreproachable manner. An appended set of questions referring to the contents of each chapter makes the book well suited for group reading and teaching.

This is one of the most excellent popular books on psychology and mental hygiene. But the authors go a little bit too far when they feel that this (or any other) book could be used by "patients suffering from nervous or even mental disorders . . . as a map or chart" by which they can be "enabled to struggle out of the mazes of suffering and difficult living." No book can do that.

L. K.

Behavior and Neurosis. By JULES H. MASSERMAN. 269 pp. Illus. $3.00. The University of Chicago Press, Chicago, 1943.

This is a curious book. Beginning with a reference to ancient Greek mythology, it contains a thrillingly excellent historical introduction, a report of the author's original and sometimes ingenious cat experiments, a truly illuminating discussion of hypothalamic function, much valuable and on the whole well-integrated informa-

tion on the literature on experimental studies of behavior and neuroses, and a discussion of clinical and psychotherapeutic applications of . . . Of what?

The book is subtitled: An Experimental Psychoanalytic Approach to Psychobiologic Principles. There can hardly be a more exciting promise. But this reader, arriving at the last page, felt as a child must feel who, having been made to expect an ice cream cone, is given a dish of warmed-over spinach instead. Mere translations of time-honored concepts and practices into a certain type of terminology do not constitute an approach or an explanation. Assertion of belief, however fascinatingly and enthusiastically expressed, does not carry the weight of scientific proof. The author could have profited a greal deal from the "aloof juridicism" which he criticizes in Adolf Meyer. Such juridicism may indeed "merely postpone the clarification of the fundamental issues involved" if one looks for the absolute and ultimate; but it does keep one soberly and humbly (not "aloofly") from assuming and professing that he knows all the answers.

This does not detract from the fact that the book has much meat. It is most stimulating in every one of its pages. Much experimental work, much reading and much thought have gone into its making. An extensive bibliography of nearly 1,000 items, each one of which has been thoroughly studied, gives one an idea of the author's encyclopedic knowledge and detailed preparations.

A book worth reading, thinking about, and possessing.

L. K.

Primer of Allergy. By WARREN T. VAUGHAN. 2nd ed. 176 pp. Illus. $1.75. The C. V. Mosby Company, St. Louis, 1943.

There have been no fundamental changes in the second edition of this book. A new chapter, "Learn to Live with your Allergy", formerly published in "Life and Health" magazine, has been added. There have been additions in the Questions and Answers section and in the chapter dealing with directions to the patient. The volume continues to serve excellently as an aid to the allergic patient in the better understanding of his strange malady.

E. L. K.